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Contents

Does Endovascular Perfusion Affect In-Hospital Prognosis in Q-Wave AMI Patients Within the First Hours of the Disease?

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Moscow City Center of Interventional Cardioangiology, Moscow, Russia

Despite the significant success in diagnostics and treatment of acute myocardial infarction (MI), in-hospital mortality from this disease in Russia remains high (16-20%) (1, 2, 3). One of the possible reasons for such unsatisfactory statistics is insufficiently wide and uncommon use of the most effective methods of AMI diagnostics and treatment in our country. For example, it is already well known, that urgent coronary angiography and, in case with appropriate indications, endovascular myocardial reperfusion significantly improves the prognosis in such patients and decreases both in-hospital and long-term mortality rates (4, 5, 6, 9). Due to wide use of these methods of AMI diagnostics and treatment, the in-hospital mortality rate decreased from 12% to 3-4% in the Scientific and Practical Centre of Interventional Cardioangiology.

Meanwhile, many clinics in our country including those possessing X-ray surgical diagnostics and treatment methods do not strive to maximally wide usage of the early myocardial reperfusion in AMI patients giving way only to classical medical methods of treatment of this disease.

Therefore, we consider that the important objective of practitioners and health care organizers is wide promotion of advantages of modern effective AMI treatment methods, including reperfusion therapy. This is an important part of the evidence based medicine.

With this purpose we performed a study aimed at a retrospective comparative analysis of the clinical course and outcome in AMI patients who received the reperfusion therapy within the first hours of the disease and those who received medical therapy only.

CLINICAL CHARACTERISTICS OF PATIENTS AND METHODS OF THE STUDY

The study included two groups of Q-wave AMI patients treated in Moscow City Center of Interventional Cardiology during the period from October 2004 till October 2008. This period of time was chosen due to the fact that the protocol of diagnostics and treatment of Q-wave AMI patients did not change significantly during this time i.e. it was standardized.

The first group consisted of 529 Q-wave AMI patients who underwent selective coronary angiography and therapeutic endovascular procedures to achieve myocardial reperfusion together with common methods of diagnostics and treatment. In the majority of cases (70.1%) these procedures were performed urgently within the first hours of the disease. In other patients the procedures were performed in later period of in-hospital stay. The early post-MI angina or other clinical and laboratory signs of continuing myocardial hypoxia were the indications for procedure delay.

The second group consisted of 335 Q-wave AMI patients who did not underwent selective coronary angiography and endovascular therapeutic procedures (patients' refusal, iodine and X-ray contrast agents' intolerance, absence of functioning angiography service during employees' vacations or some holidays).

There were no significant differences between the compared groups in baseline clinical, laboratory and historical data (Table 1).

Table 1. Baseline Clinical Characteristics.

PARAMETER	GROUP 1 endovascular treatment (n=529)	GROUP 2 medical therapy (n=335)	p
Mean age	54.6±9.2	56.1±10.3	p>0.05
Number of male patients	456 (86.2%)	273 (81.5%)	p<0.05
Hypertension	346 (65.4%)	239 (71.3%)	p<0.05
Smoking	328 (62%)	186 (55.5%)	p>0.05
Diabetes mellitus	60 (11.3%)	40 (11.7%)	p>0.05
Hypercholesterolemia	342 (64.7%)	201 (60.0%)	p<0.05
Previous MI	78 (14.7%)	65 (19.4%)	p<0.05
TLT (systemic)	100 (18.9%)	41(12.2%)	p<0.05
Q-wave MI	529 (100%)	335 (100%)	p<0.001
LV EF, %	52.6±12.2	49±12.9	p<0.05
Time from the attack onset	5 (0.9%)	9 (2.7%)	p<0.05
up to 24 hours:	372 (70.3%)	245 (73.1%)	p<0.05
< 6 hours	209 (39.5%)	125 (37.3%)	p<0.05
6-24 hours	163 (30.8%)	120 (35.8%)	p<0.05

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AMI diagnosis was established according to common Minnesota Code criteria (10), cases of recurrent MI were considered as well. During data analysis a history of previous myocardial infarction, diabetes mellitus, hypertension were taking into consideration. In the cardiac intensive care unit AMI patients were treated according to the developed protocol including nitrates infusion therapy, beta-blockers, platelet aggregation inhibitors, ACE inhibitors and in some cases calcium antagonists. In some patients (N=141) systemic thrombolysis was performed at pre-hospital stage. In the 1st group the number of such patients was significantly higher, but it should be noted that according to coronary angiography data, thrombolysis was ineffective in these patients.

Patients of the 1st group who were admitted to hospital within the first hours from the onset of anginal attack underwent urgent coronary angiography and in case of stenotic or occlusive lesion of the coronary arteries the endovascular procedure of blood flow restoration in the infarct-related artery (IRA) was performed (fig.1)

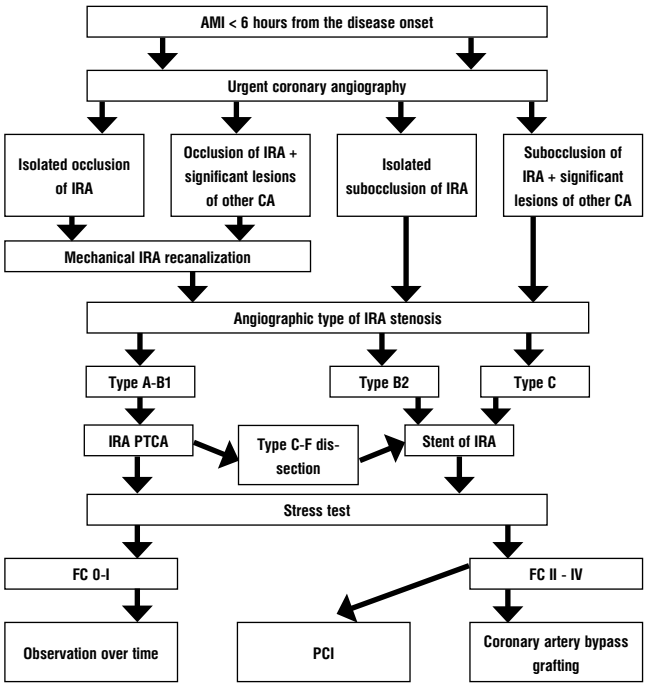

Figure 1 . Algorithm of treatment within the first hours of AMI.

ECG monitoring was performed in all MI patients that allowed to assess blood pressure, heart rate, respiratory rate, and pulsoxymetry values. After stabilization patients were transferred to the myocardial infarction department for further treatment and examination.

Statistical procession of the study results was performed using standard non-parametric statistical methods: Mann-Whitney test for comparing means, Fisher's exact test and Spearmen correlation analysis (significance level $p<0.05$).

STUDY RESULTS AND DISCUSSION

In group 1 immediate angiography success of endovascular procedures (PCI) (residual stenosis up to 30% in patients with PTCA and up to 20% in case of stenting, absence of type C-F dissection and distal embolization, antegrade blood flow restoration TIMI 2-3) was high, up to 518 (97.9%). In 11 (2.1%) cases IRA stenting was accompanied by distal embolization and in another 9 (1.7%) patients early post-operative stage was complicated by recurrent angina with ECG changes, and control coronary angiography revealed the threatening vessel intima dissection in PTCA/ stenting site requiring the use of additional stent. Antegrade blood flow TIMI 2 after the procedure was noted in 35 (6.6%) patients, the rate of residual stenosis was 12.1±16.2% and did not exceed 30%, vessel edges at the site of plasty were smooth and regular without stenotic changes. The results of disease treatment at in-hospital stage in groups of endovascular and medical treatment are presented in Table 2.

Table 2. In-Hospital Treatment Results In Examined Groups.

PARAMETERS	Group 1 (n=529)	Group 2 (n=335)	p
- ANGINA PECTORIS	32 (6.1%)	60 (17.9%)	0.001
- RECURRENT MI (non-fatal)	8 (1.5%)	25 (7.5%)	0.04
- CF (Killip class I-III),	66 (12.5%)	77 (23.0%)	0.001
MORTALITY:			
total	11 (2.1%)	39 (11.6%)	0.001
ardiac causes	7 (1.3%)	35 (10.5%)	0.001
THROMBOSIS/IRA REOCCUSION*	21 (4.0%)	-	-
URGENT REPEATED/PRIMARY IRA PTCA:	29 (5.5%)	-	-
- thrombosis/reocclusion	20 (3.8%)	-	-
- dissection	9 (1.7%)	-	-
ELECTIVE PCI on other CA (not IRA)	11 (2.1%)	-	-
NON CORONARY COMPLICATIONS (non fatal):			
Cerebrovascular disorders (CVA)	3 (0.6%)	6 (1.8%)	>0.05
- GIB	7 (1.3%)	4 (1.2%)	>0.05
Haematoma at the puncture site	7 (1.3%)	-	-
- Pulmonary embolism	1 (0.2)	3 (0.9%)	>0.05
Smooth course of the disease**	400 (75.6%)	124 (37%)	0.0001

* Stent thrombosis and reocclusion after PTCA in group 1. Patients with fatal outcome and recurrent AMI are included.
** Absence of fatal cases, recurrent AMI, early post-infarction angina, CF (Killip class I-III), GIB and PE cases and cerebrovascular complications.

Smooth clinical course after intervention (without mortality, recurrent MI, angina reappearance, CF I-III (Killip class), CVA, PE, hematomas and internal bleeding requiring hemotransfusion or surgical intervention) was observed in 400 (75.6%) patients of group 1 and in 124 (37%) patients of group 2 ($p< 0.05$). Thus, PCI use in AMI patients allowed for a significant increase of the clinical success rate from 37% in conservative medical therapy to 75.6% in case of additional endovascular treatment.

In group 1 severe complications such as thrombosis/reocclusion of IRA were revealed in 21 (4.0%) cases: one patient (0.2%) died despite the undertaken resuscitation and endovascular measures, in

8 (1.5%) cases non fatal recurrent MI developed and in another 12 (2.2%) patients with prolonged angina attack and IRA subocclusion there was no evidence for myocardial damage. Successful repeated PCI with antegrade blood flow restoration TIMI 3 and further eventless course of disease were performed urgently in all 20 (3.8%) patients with IRA thrombosis and in 9 (1.7%) patients with clinical signs of unstable angina and dissection after primary angioplasty. In other 11 (2.1%) patients with clinical signs of unstable angina, multiple CA lesions and preserved good angiographic effect of PCI on the IRA, elective angioplasty procedure was performed on other coronary arteries. **In group 2,** 25 (7.5%) patients versus 8 (1.5%) in the group of PCI developed non-fatal recurrent MI ($p<0.05$), 60 (17.9%) patients versus 32 (6.1%) in the PCI group had angina recurrence, 19 (38.0%) versus 3 (6.0%) patients in PCI group died of increasing circulatory failure and CABG.

Thus, the main cause of cardiac complications (including mortality) at in-hospital stage was IRA thrombosis/ reocclusion. As a rule, it leads to recurrent MI and death. **The performed analysis** of stent thrombosis lesions revealed significant relationship with the following risk factors: 1) restored blood flow TIMI 2, 2) urgent bailout stenting in case of standard balloon angioplasty – 1) residual stenosis > 30%, 2) type C-F dissection, 3) type B2-C stenosis, 4) LV EF <40%, 6) dyskinesia with formation of large aneurism.

In addition to IRA thrombosis / reocclusion severe complications such as PE (n=4), GIB (n=11), ischemic or hemorrhagic stroke (n=9) and hematoma or internal bleeding requiring hemotransfusion or surgical intervention (n=7) were observed in the examined groups. Herewith, 3 out of 4 patients with PE and 5 out of 11 patients with GIB the disease died. According to autopsy data, PE and GIB were the main causes of death in these 8 patients.

Thus, during in-hospital stage 50 (5.8%) out of 864 AMI patients died: in 42 (4.8%) cases the death was heart-related and in 8 (0.9%) - non cardiac. The analysis of fatal outcomes analysis at in-hospital stage in the groups of endovascular and medical treatment is presented in Table 3.

Cardiac mortality in the group of endovascular treatment was 7 (1.3%), which was significantly lower then that in group 2 (medical treatment) – 35 (10.5%) ($p=0.0001$). Significance of differences persisted both in patients hospitalized within the first hours from the disease onset - 6 (1.6%) versus 30 (12.2%), and in patients hospitalized within 24 hours - 21 days - 1 (0.6%) versus 5 (5.5%) cases, respectively ($p=0.0001$).

The main causes of cardiac mortality at in-hospital stage were cardiogenic shock (n=11), myocardium rupture with subsequent cardiac tamponade (n=14), circulation failure (Killip class II-III) refractory to treatment (n=11), complex rhythm and conduction disturbances (VF) refractory to electroimpulse therapy and electrocardiostimulation – (n=5) and stent thrombosis /IRA occlusion after unsuccessful effort of EVT (n=1).

Table 3. Analysis of in-hospital mortality in the examined groups.

Parameter	GROUP 1 endovascular treatment (n=529)		GROUP 2 medical therapy (n=335)		P <0.05
	Group 1A <24 hour (n=372)	Group 1B 24 hours 21 days (n=157)	Group 2 A <24 hour (n=245)	Group 2B 24 hours 21 days (n=90)	
Survival	518 (97.9%)		296 (88.3%)		For group1 – group 2
Mortality (total)	11 (2.1%)		39 (11.6%)		For group1 – group 2
	10 (2.7%)	1 (0.6%)	34 (13.9%)	5 (5.5%)	For 1A – 2A For 1B – 2B
Mortality (cardiac)	7 (1.3%)		35 (10.5%)		For group1 – group 2
	6 (1.6%)	1 (0.6%)	30 (12.2%)	5 (5.5%)	For 1A – 2A For 1B – 2B
Causes: - cardiogenic shock - myocardium rupture	1 (14,3%) 2 (28,6%)		10 (28,6%) 12 (34,3%)		For group 1-2 For group 1-2
- CF (Killip class II-III)	2 (28,6%)		9 (25,7%)		NS
- ventricular fibrillation (VF)	1 (14,3%)		4 (11,4%)		NS
- stent/IRA thrombosis (unsuccessful EVT effort)	1 (14,3%)		-		-

In order to detect the factors that can affect AMI mortality at in-hospital stage, we performed statistical analysis of a major part of clinical, laboratory and historical data of these patients. Such variables as age, arterial hypertension, dyslipidemia, smoking, diabetes mellitus, previous MI, localization and severity of lesion, presence of early post-infarction angina, recurrent MI, methods of treatment used (medical and endovascular) were analyzed taking into consideration time of revascularization.

The analysis performed with the use of exact Fisher's test demonstrated significant correlation of fatal outcome with the method of treatment (medical therapy), circular myocardium infarction, history of post-infarction cardiosclerosis and diabetes mellitus, cardiogenic shock, low LV EF (<40%), arterial hypotension (< 100 mm Hg), tachycardia (> 100 bpm), three vessel lesion, CFC >1000 U. In addition, correlation analysis demonstrated significant inverse relationship between hospital mortality and early post-MI rate, on the one hand, and proportion of successful endovascular procedures performed in early terms of AMI, on the other hand ($R=-0.95$, $p<0.00003$ and $R=-0.95$, $p<0.00003$, respectively).

Besides, performed analysis revealed elderly age (> 65 years) and female gender to be predictors of cardiac mortality, but only for patients of group 2 (medical therapy). In general, this is consistent with existing opinion that elderly age and female gender are the risk factors for complications development and hospital AMI mortality (8). However, in this study there were no significant differences in the group of

endovascular treatment between patients under 65 years and over 65 years in number of fatal cases and other cardiac complications, as well as between men and women.

In general, analysis of hospital mortality demonstrated higher efficacy of endovascular AMI treatment allowing not only for the restoration of coronary blood flow in the IRA but for cardinal reduction of the reperfusion time. Obtained data confirm the existing opinion that the reduction of coronary blood flow restoration time allows to shorten maximally the myocardium damage and thereby to improves immediate (hospital) disease prognosis (7).

Thus, PCI performance in addition to standard medical therapy in AMI patients both early (to 24 hours) and in delayed period (24 hours – 21 days) significantly improves clinical outcome of disease, allows to significantly decrease cardiac mortality, risk of development of recurrent AMI, early post-infarction angina and cardiac failure. Moreover, PCI in AMI patients allows to decrease the duration of the hospital stay from 19.2 days with conservative therapy to 12.1 days in case of endovascular treatment.

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Reperfusion Therapy in Acute Coronary Syndrome with ST Elevation

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Keywords: acute coronary syndrome with elevation of ST-segment, reperfusion therapy, systemic thrombolysis, transluminal balloon angioplasty, left ventricle systolic and diastolic parameters.

INTRODUCTION

Over the last years, great attention is paid worldwide to investigation of pathophysiology and treatment options for acute coronary syndrome. Unstable angina, non-Q-wave myocardial infraction are currently combined in the concept of "acute coronary syndrome" – a condition that develops acutely in patients with coronary heart disease (1, 2), and has common morphologic basis: atherosclerotic plaque rupture, plaque hemorrhage, or rarely, loss of plaque endothelium integrity associated with increased blood coagulation activity (hypercoagulation and platelet aggregation), which leads to blood clot formation at the site of this rupture or to coronary endothelial defect (3-6). In addition to friable clot formation, a certain role in acute coronary syndrome belongs to inflammation within the vessel wall near plaque basis (6). Intravascular phenomena observed in acute coronary syndrome only differ in stenosis degree and duration of coronary blood flow disturbance. Often no clear differentiation can be made between unstable angina and non-Q-wave myocardial infraction (7). The creation of wide network of intensive care departments and advancement of used techniques: prevention and treatment of life-threatening heart rhythm disturbances, treatment of acute heart failure, and thrombolysis allow to significantly decrease in-hospital mortality from myocardial infarction. However, the extension of myocardial infarction and mortality can only be managed approximately within the first 6 hours from its onset, whereas the majority of patients are hospitalized significantly later. 30-40% of the total number of patients die within the first 15 minutes from the onset, and the similar number of patients die within the next two hours. It means that two thirds of deaths occur before admission to hospital, even with well-organized emergency care. That's' why hospitalization and intensive treatment in the period before ACS development is one of the most important methods for decreasing ACS mortality. The main objective of modern cardiology studies is selection of ACS pathogenesis therapy considering the hazard of ACS as an acute form of CAD. Based on the nature of disturbances in ACS, antithrombotic therapy is the first step in ACS therapy. To date, the positive effect of systemic thrombolysis in patients with ST elevation ACS is obvious. Thrombolysis performed within the first two hours from anginal attack onset allows to achieve blood flow restoration and reversion of MI. Thrombolysis, even performed later, allows reducing myocardial necrosis area, although not preventing myocardial necrosis development, and allows to prevent delayed aneurism formation and heart failure following MI. Recently, important achievements were made in the field of revascularization, including percutaneous transluminal coronary balloon angioplasty (PTCA) – fundamentally new technique. The nineties of the last century were the "blooming" decade for percutaneous coronary interventions. Today, more than 800 patients per million population are annually treated using this technique in economically developed countries of Europe, which exceeds the use of conservative therapy and coronary artery bypass graft surgery. Thus, the treatment of ACS patients is the leading edge of modern cardiology not only due to wide disease prevalence, but due its tragic significance.

The objective of this study was to investigate an effect of PTCA versus systemic thrombolysis on central and intracardiac hemodynamics in ACS.

MATERIALS AND METHODS

Eighty patients hospitalized in the Department of Cardiac Intensive care Unit of the Republican Scientific Centre of Emergency Care and diagnosed with ST elevation ACS were enrolled in this study. Mean age of patients was 53.9±9.3 years. Time from pain onset to admission to the clinic was 8.3±8.7 hours. The patients with diabetes mellitus, who had myocardial infarction or cerebral vascular accident, LV aneurism, atrial flutter, left bundle branch block, significant organ insufficiency and cardiomyopathies were excluded from the study.

All patients underwent echocardiography (EchoECG) and Doppler echocardiography (Doppler EchoECG) on admission, on Days 3 and 7 to assess functional state of the left heart. EchoECG was performed in M- and B- modes with patients lying on their left side in accordance with American Society

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of Echocardiography (ASE) guidelines (7,3). The following parameters were measured by M-mode echocardiography in the parasternal long axis plane (4): Left atrium (LA) diameter, LV end-diastolic and end-systolic dimensions (LV EDD, LV ESD), systolic and diastolic interventricular septum thickness (IVST) and posterior left ventricular wall thickness (PLVWT). Impulse Doppler EchoECG was performed during B-mode EchoCG. Transmitral and transaortic blood flow were recorded in the apical 5- or 4-chamber view. Peaks of early and atrial filling (PE and PA, m/sec) were recorded on the mitral valve. EchoCG and Doppler EchoECG were performed using Siemens Sonoline Omnia ultrasound apparatus (Germany) with 2-4 MHz multifrequency sensor. Blood pressure (PB) was measured by N.S. Korotkov method, mean BP was calculated by Hickam formula (1).

Depending on performed reperfusion therapy, patients were assigned into 2 groups. Patients from Group I (55 patients) underwent coronary transluminal balloon angioplasty and patients from Group II (25 patients) underwent systemic thrombolysis (STL) with streptokinase at a dose of 1 500 000 U IV over one hour in order to achieve reperfusion.

All patients enrolled in the study received an appropriate treatment in accordance with recommendations of American Heart Association and American College of Cardiology (2001) including anticoagulants (heparin), antiaggregants (clopidogrel, ticlopidine and aspirin), beta-adrenoblockers (atenolol, metoprolol), nitrates, analgetics (neuroleptanalgesia). Statistical processing of the data obtained from this study was performed on personal computer using EXCEL 7.0 for WindowsXP.

Correlation and regression analysis methods were used. All values in the tables are presented as arithmetic mean of variational series ± standard deviation. Alternative hypothesis with significance level no less than 95% (p=0.05) was used as statistic hypothesis. All parameters were subject to the normal distribution. Paired and two sample Student t-test were used to test the hypothesis of equality of means.

RESULTS AND DISCUSSION.

Statistical comparison of intergroup differences in changes of the studied parameters over time revealed (Fig.1), that the impact of studied reperfusion methods differs only in the effect on LV EF ($p<0.05$). EF change over time in PTCA group (15,08% on Day 7) was significantly better than that in STL group (4.84%, $p<0.01$).

On Day 3 blood pressure was significantly lower in PTCA group (SBP reduced by 1.58%, $p<0.05$, DBP reduced by 4.35%, $p<0.001$), which was probably related to the therapeutic methods used (Table 1). Although heart chamber dimensions did not change significantly over the specified period, significant improvement of LV systolic function was observed as early as on Day 3, i.e. LVEF increased by 7.52% ($p<0.01$). This was due to decrease in LV ESD by 1.91% ($p<0.05$), while EDV had insignificant tend to decreased (by 0.36%, NS). Maximal blood flow on the aortic valve also increased significantly (by 5.10%, $p<0.01$), this fact confirms significant improvement of LV systolic properties. The active diastolic LV filling rate increased by 6.71% ($p<0.05$), suggesting improvement of active diastolic LV relaxation processes, possibly caused by the decrease in calcium-mediated cellular resetting in ischemic myocardium. The number of patients with decreased LVEF reduced from 41 (73.2%) to 38 persons (67.9%, NS). The described changes have continued further. At the end of Days 5-7 LV EDV and ESD reduced by 3.33% ($p<0.05$) and 3.42% ($p<001$), respectively, leading to EF increase by 15.08% ($p<0.001$), however, stroke volume was not changed significantly. The improvement of myocardial systolic functions confirms the increase in aortic peak ejection rate (by 3.66%, $p<0.01$). Active diastolic LV filling rate increased by 7.84% ($p<0.05$) compared to baseline, suggesting the tendency to further improvement of active diastolic function compared to Day 3 findings. Blood pressure was stabilized. The comparison of change in the studied parameters on Days 1-3 and 1-7 revealed significantly better effect of used therapy on LV ESD on Days 5-7 compared to Day 3 (-3.42 versus -1.91%, $p<0.01$), EDV (-3.33 versus NS change, $p<0.05$) and EF (15.08 versus 7.52%, $p<0.001$). The effect on DBP was significantly lower (-1.68 versus -4.35%, $p<0.05$). Patient distribution by geometric parameters revealed that the number of patients with decreased EF at the end of Day 7 was 30 persons (53.6%) versus 41 persons (73.2%) on admission, respectively, ($p<0,05$). LV dilatation initially observed in 16 (28,6%) patients was still present in 15 (26.8%, NS) patients at the end of observational period, and LA dilatation was observed in 6 (10,7%) and 5 (8.9%, NS) patients, respectively. Type I diastolic dysfunction initially observed in 30 (53.6%) patients was still present in 19 (33.9%, $p<0.05$) patients at the end of observational period.

In STL group, the studied parameters changed over the treatment as follows (Table 2): Heart chamber dimensions and absolute LV wall thickness did

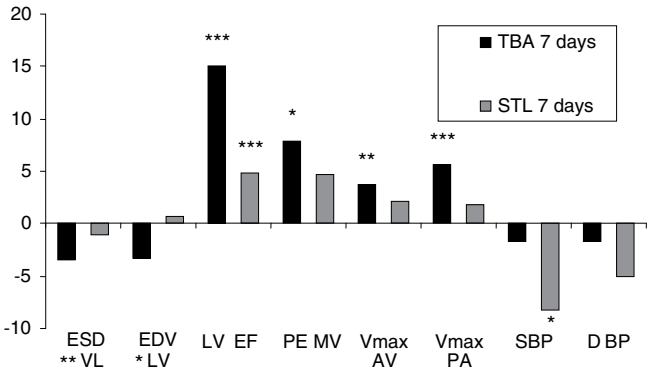

Figure 1. Comparison of change in the studied parameters over 7 days with the use of different methods of myocardial reperfusion in ST-elevation ACS patients.

Note: The degree of certainty of change in parameters over time: *p<0.05, **p<0.01, ***p<0.001

Table 1. Change over time in Doppler EchoCG parameters in PTCA-treated ST-elevation ACS patients.

Parameter	Baseline	Day 3	Day 5-7
LA, cm	3.61±0.34	3.61±0.34	3.62±0.33
ESD, cm	3.93±0.44	3.84±0.44*	3.78±0.44**
EDD, cm	5.26±0.39	5.25±0.39	5.20±0.37
EDV, mL	131.83±25.24	131.72±23.72	125.67±21.59*
SV, mL	64.39±14.00	67.06±12.74	64.80±11.91
EF, %	48.87±7.11	51.64±5.86**	54.72±4.16***
MV PE, m/sec	0.66±0.09	0.69±0.08*	0.70±0.09*
MV PA, m/sec	0.67±0.09	0.66±0.10	0.68±0.09
Vmax Ao, m/sec	0.90±0.09	0.94±0.10**	0.93±0.08**
TV PE, m/sec	0.51±0.05	0.51±0.06	0.51±0.06
TV PA, m/sec	0.43±0.04	0.43±0.04	0.43±0.04
Vmax PA, m/sec	0.73±0.06	0.75±0.07	0.77±0.08***
SBP, mmHg	132.16±17.22	127.86±7.60*	127.14±5.71
DBP, mmHg	81.66±8.70	77.05±5.15***	78.75±4.24

Note: The significance of differences from pre-treatment parameters: *p<0.05, **p<0.01, ***p<0.001

Table 2. Change over time in Doppler EchoCG parameters in SLT-treated ST-elevation ACS patients.

Parameter	Baseline	Day 3	Day 5-7
LA, cm	3.45±0.31	3.44±0.43	3.43±0.30
ESD, cm	3.71±0.27	3.66±0.36*	3.66±0.23
EDD, cm	5.01±0.42	5.01±0.61	5.04±0.40
EDV, mL	127.06±16.67	124.74±24.41	126.73±15.00
SV, mL	67.01±10.38	66.37±12.95	68.14±10.48
EF, %	52.71±3.62	54.32±4.37**	55.02±3.28***
MV PE, m/sec	0.68±0.06	0.72±0.11	0.71±0.08
MV PA, m/sec	0.79±0.07	0.77±0.13	0.77±0.08
Vmax Ao, m/sec	0.91±0.04	0.96±0.08***	0.93±0.04
TV PE, m/sec	0.49±0.02	0.51±0.04	0.51±0.04
TV PA, m/sec	0.42±0.02	0.43±0.03	0.43±0.02
Vmax PA, m/sec	0.65±0.05	0.66±0.07	0.65±0.04
SBP, mmHg	138.76±21.21	131.40±15.65*	129.57±9.58*
DBP, mmHg	85.24±12.89	81.20±8.33	81.52±4.59

Note: The significance of differences from pre-treatment parameters: *p<0.05. **p<0.01. ***p<0.001

not change significantly over 5 days of observation; SBP decreased significantly at the end of Day 3 (by 3.46%, p<0.05) and continued to decrease after that (by 8.27% at the end of Day 7, p<0.05); DBP showed non-significant tendency to decrease; LV systolic function improved significantly demonstrating EF increase by 3.88% (p<0.01) and 4.84% (p<0,001) at the end of Days 3 and 7, respectively. EF change over Days 5-7 was significantly better than that on Day 3 (4.84 versus 3.52%, p<0.01). EF increase was caused by decrease in LV ESD by 1.03% (p<0.05) at the end of Day 3. The increase in the effectiveness of systolic contractility is manifested as an increase in maximal aortic ejection rate (by 5.33%, p<0.001), however, this parameter is slightly reduced at the end of Days 5-7, still remaining higher than baseline values. LV and RV diastolic function show the tendency to increase in the early LV diastolic filling rate, and LV FR redistribution favouring the early filling, however, not achieving the significance criteria, and further, by the end of Days 5-7, maximal early filling rate is slightly reduced. Initially, the number of patients with decreased EF was 16 (64%), at the end of Day 3 - 11 persons (44%, NS), and at the end of Days 5-7 - 9 persons (36%, p<0.05). Diastolic dysfunction was observed in 22 (88%), 20 (80%), and 16 (64%) patients, respectively (NS).

ACS transformation into one or another nosology occurred as follows: in PTCA group 37.5% patients developed Q-wave MI, 30.4% patients developed non-Q-wave MI, and 33.9% patients developed unstable angina. In STL group all patients without exception developed Q-wave MI.

Thus, as the conducted study has shown, different methods of reperfusion therapy in ACS patients allow to improve significantly the heart systolic function and contribute to normalization of LV diastolic function in the absence of changes in anatomic dimensions of the heart as early as within the first 24 hours of disease. The comparison of the studied methods revealed significantly better positive effect. This study has shown that all studied reperfusion methods significantly improve LV systolic parameters by increasing LV EF and the systole efficacy (increase in maximal aortic ejection rate). Increase in LV EF in PTCA group was significantly higher than that in STL group. Moreover, PTCA significantly improves the active diastolic myocardial function, while in STL group MV PE was changed non-significantly. However, intergroup comparison of changes in MV PE over time revealed no significant difference in the effect.

CONCLUSIONS

1. Use of PTCA in ST-elevation acute coronary syndrome leads to fast improvement of left ventricle global contractility.
2. Active diastolic myocardial function improved significantly as early as at the end of the first week after PTCA in contrast to systemic thrombolysis group where this parameter demonstrated only a trend to improvement.

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Stent-Graft Repair in Acute and Chronic Diseases of the Thoracic Aorta

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INTRODUCTION

Aneurysmal conditions of the descending thoracic aorta represent a potentially life-threatening situation with a risk of rupture depending on diameter (1). Surgical resection and interposition of vascular prostheses have long been considered the standard of care despite substantial risk of adverse events and complications from surgical trauma (2). Regardless of recent strides to improve technique and management, operative mortality and morbidity remained high. As a consequence of demographic changes in the Western world, the population is aging and associated with a variety of comorbidities portending an inherent risk and explaining in part the sobering surgical outcomes with perioperative complications contributing to prolonged hospitalization and high costs (3). As a revolutionary alternative, the concept of an endoluminal stent-graft in patients with thoracic aortic disease has emerged a decade ago propelled by the desire to avoid surgical risks by use of a nonsurgical approach and to induce reconstructive remodelling of the diseased aorta by initiating a natural healing process through exclusion and depressurization of the aneurysmal sac (4-6). Although initial reports on the endovascular stent-graft strategy were encouraging in various pathologies (3, 7-9), randomized data are still limited, and smouldering critique has never been fully extinguished because of lacking long-term follow-up data.

Early clinical experiences with stent-grafting of the thoracic aorta were based on the use of home-made devices that were rigid and required large delivery systems (4). To date, several companies obtained approval for commercial release of their thoracic endografts in the U.S. and Western Europe, and it is likely that other devices will follow them in the marketplace (10-13). Although each device has unique features, all employ the same basic structural design (Figure 1). Generally, endoprotheses are composed of a stent (nitinol or stainless steel) covered with fabric (polyester or PTFE); different designs are available to facilitate endoluminal fixation (bare/covered springs or barbs). The selection of patients on the basis of favourable anatomy and pathology for a specific endovascular device is key to the success of the procedure. Not all patients have lesions amenable to endovascular repair, and thoracic endografting is technically challenging, requiring dedicated facilities and experienced specialists. Conversely, shortcomings of specific endovascular devices including device collapse, migration or unprecise launching are not fully resolved (14). This article reviews current indications and advancing fields of endovascular repair in the thoracic aorta.

ENDOVASCULAR RECONSTRUCTION OF THORACIC AORTIC DISSECTION

Stent-grafting as an emerging option in type B dissection

The optimal treatment strategy for patients with aortic dissection confined to the descending aorta (Stanford type B) remains a matter of debate (15). Despite continuous efforts for improvement, surgical resection of dissection is still associated with operative mortality ranging between 0 and 27% in elective cases, and exceeding 50% in complicated dissection under emergency conditions (16). Given such grim outlook with open surgery, there is consensus that patients with type B aortic dissection should primarily be treated medically with tight blood pressure control, while reserving endovascular surgery for evolving complications (e.g. recurrent pain, progressive false lumen expansion, malperfusion or imminent rupture) (17). In a recently published series of 384 patients with acute type B dissections from IRAD, 73% were managed medically with an in-hospital mortality of 10% (18). However, even without complications in acute stage, the long-term prognosis of type B dissection was sobering with a reported 3 year mortality of 20-40% despite optimal medical and surgical therapy (19).

In 1999, the concept of endovascular stent-graft implantation was introduced as a novel treatment option propelled by the idea to seal the proximal entry tear, remodel the aorta and avoid risk of open surgery (20,21). This rationale was originally based on the clinical observation that patients with spontaneous thrombosis of the false lumen have a better long-term prognosis (22). Conversely, perfusion of the false lumen has been identified as an independent predictor of progressive aortic enlargement and adverse long-term outcome (23). Several single-centre reports and multinational registries have cor-

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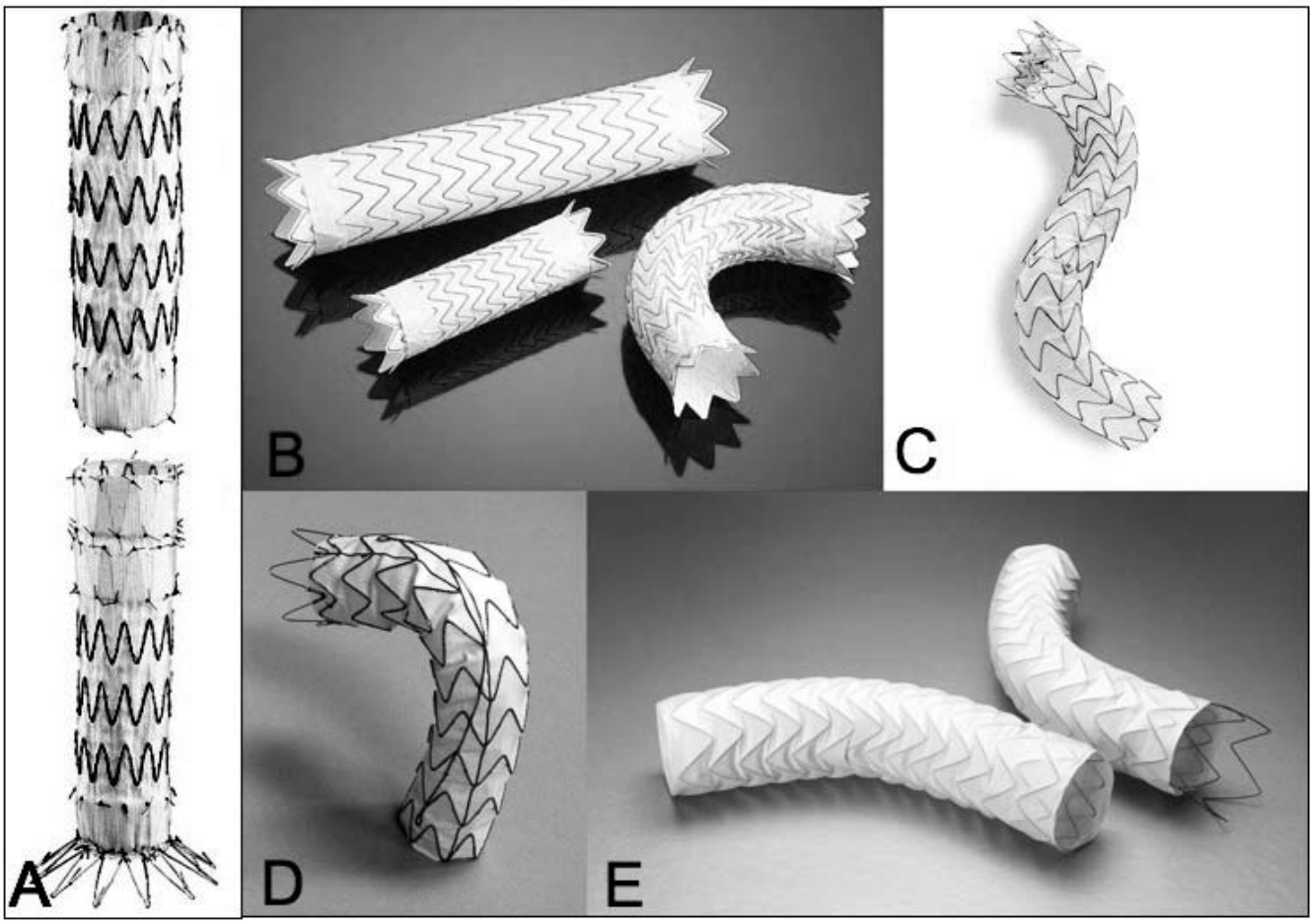

Figure 1. A selection of thoracic stent-grafts currently available for endoluminal repair. Zenith TX2 by Cook Medical (A), TAG by GORE (B); Valiant by Medtronic AVE (C) ; Relay Thoracic Stent-Graft by Bolton Medical (D); EndoFit by LeMaitre Vascular (E).

roborated technical feasibility and clinical safety of endoluminal thoracic aortic reconstruction in type B dissection, but final data from randomized trials are not available yet (7-9).

The mechanics of endovascular repair in aortic dissection

The natural course of aortic dissection is characterized by a continued false lumen expansion carrying the risk for late rupture (24). The most effective method to exclude an enlarging false lumen in type B dissection is to seal the proximal entry tears with a customized stent-graft (20,21). Depressurization and shrinking of the false lumen is the most beneficial result to be gained, ideally followed by complete thrombosis of the false lumen and remodeling of the entire dissected aorta (25, 26). In scenarios with dynamic true lumen collapse, malperfusion syndrome may also be corrected by single thoracic endografting (27-29); in selected patients distal bare-stent extension (PETTICOAT-concept) may potentially enhance the remodeling process by enlarging the true lumen and re-establishing distal blood flow. (Figure 2). Similar to previously accepted indications for surgical intervention, scenarios such as intractable pain, rapidly expanding false lumen, diameter over 55 mm and signs of imminent rupture or distal malperfusion are now accepted indications for stent-graft placement in type B dissection(31-34). Preliminary data suggest that endovascular repair is superior to open surgery in complicated cases of type B dissection with respect to in-hospital morbidity and earl mortality (35, 36). Paraplegia generally appears to be a rare phenomenon (0.8%), but is known to be associated with extensive coverage of the aorta > 20 cm and use of multiple stent-grafts (7-9). Results of short-term follow-up are excellent with a 1-year survival rate of >90%; tears can be readapted and aortic diameters generally decrease with complete thrombosis of the false lumen. This suggests that stent-graft placement may facilitate healing of the dissection, sometimes of the entire aorta, including abdominal segments (Figure 3). However, primary endoleaks and late reperfusion of the false lumen have been observed occasionally underlining the need for stringent follow-up imaging and additional stent-graft placement in some patients (37-39). To clarify the role of prophylactic endovascular repair, final results from the randomized INSTEAD trial are awaited comparing the outcome of treating uncomplicated Type B dissection with a Talent stent-graft in addition to best medical treatment versus best medical treatment alone (40), while interim analysis has not provided a survival benefit of stent-graft therapy within a year. Stent-graft treatment in chronic type

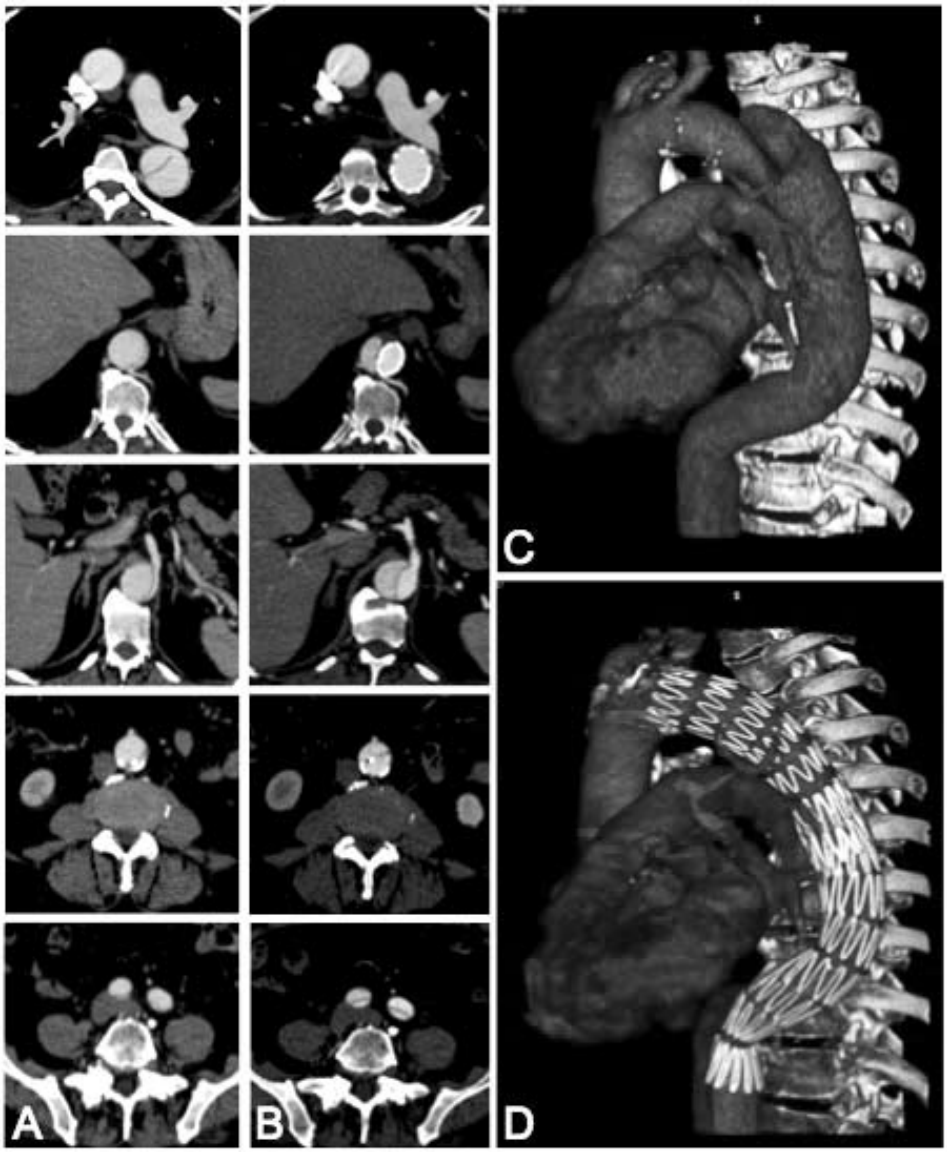

Figure 2. Endovascular treatment of acute type B dissection presenting with peripheral malperfusion (A). The composite of images depicts the PETTICOAT concept as an adjunctive distal bare-stent extension after deployment of a proximal thoracic stent-graft. Notably, occlusion of the proximal entry tear was followed by thoracic false lumen thrombosis (C, D). The metal scaffolding extension prevents true lumen collapse and ensures normalized distal run-off (B).

Endovascular approach to the proximal aorta

Two-third of patients hospitalized for aortic dissection is diagnosed with Stanford type A dissection characterized by an entry in the ascending aorta. Distal involvement is frequently observed with the dissection lamella propagating into both aortic arch and descending aorta in over 70%. Acute type A dissection is an emergency and requires swift surgical replacement of the ascending aorta; only in selected cases exclusive endovascular approach to the proximal aorta may be an option (Figure 4). According to IRAD, 92% of patients qualify for replacement of the ascending aorta; of those 23% also required partial arch and 12% required total arch replacement. Overall, 91% of patients underwent repair utilizing cardiopulmonary bypass in hypothermic circulatory arrest, while 52% were subjected to antegrade cerebral perfusion. In addition to 25% in-hospital mortality among surgically treated patients, a patent false lumen remains in the aortic arch in up to 75% of cases requiring distal reoperations in about a quarter of surviving patients (44). Considering such pessimistic outlook, type A dissection deserves reconsideration especially with emerging endovascular technology. One approach could be a staged hybrid procedure with initial replacement of the ascending aorta and simultaneous aorta-innominate artery bypass without hypothermic circulatory arrest followed by a staged left carotid bypass and transfemoral endograft to exclude the perfused distal false lumen (45). The objective of this approach is to avoid surgery on the arch with its inherent problems, but rather complete the repair with a retrograde endograft. This hybrid endovascular approach not only minimizes the risk of each surgical step, but also enables diligent evaluation of distal false lumen prior to stent-graft placement. In this setting, even single stage techniques combining open ascending tube graft insertion with simultaneous great vessel transposition and antegrade deployment of an endoluminal graft across the arch

B dissection apparently differs from acute type B pathology based on increased stiffness of the dissecting lamella and a continued false lumen expansion. Endograft deployment in chronic dissection does not necessarily focus on expansion of the true lumen, but aims to depressurize the false lumen by promoting progressive thrombosis. This remodeling process is often complicated by the rigidity of the dissecting lamella, as reflected by the higher amount of procedural failure in chronic dissection (7). Furthermore, as the individual case selection is important, some comorbidities such as connective tissue disorders and general state of health need to be considered. For instance, in Marfan patients endovascular strategies may only be justified to bridge to definite surgical repair, but failed to impact on early outcomes (41,42). Moreover, general state of health prior to endovascular therapy has demonstrated to influence postprocedural outcomes (43).

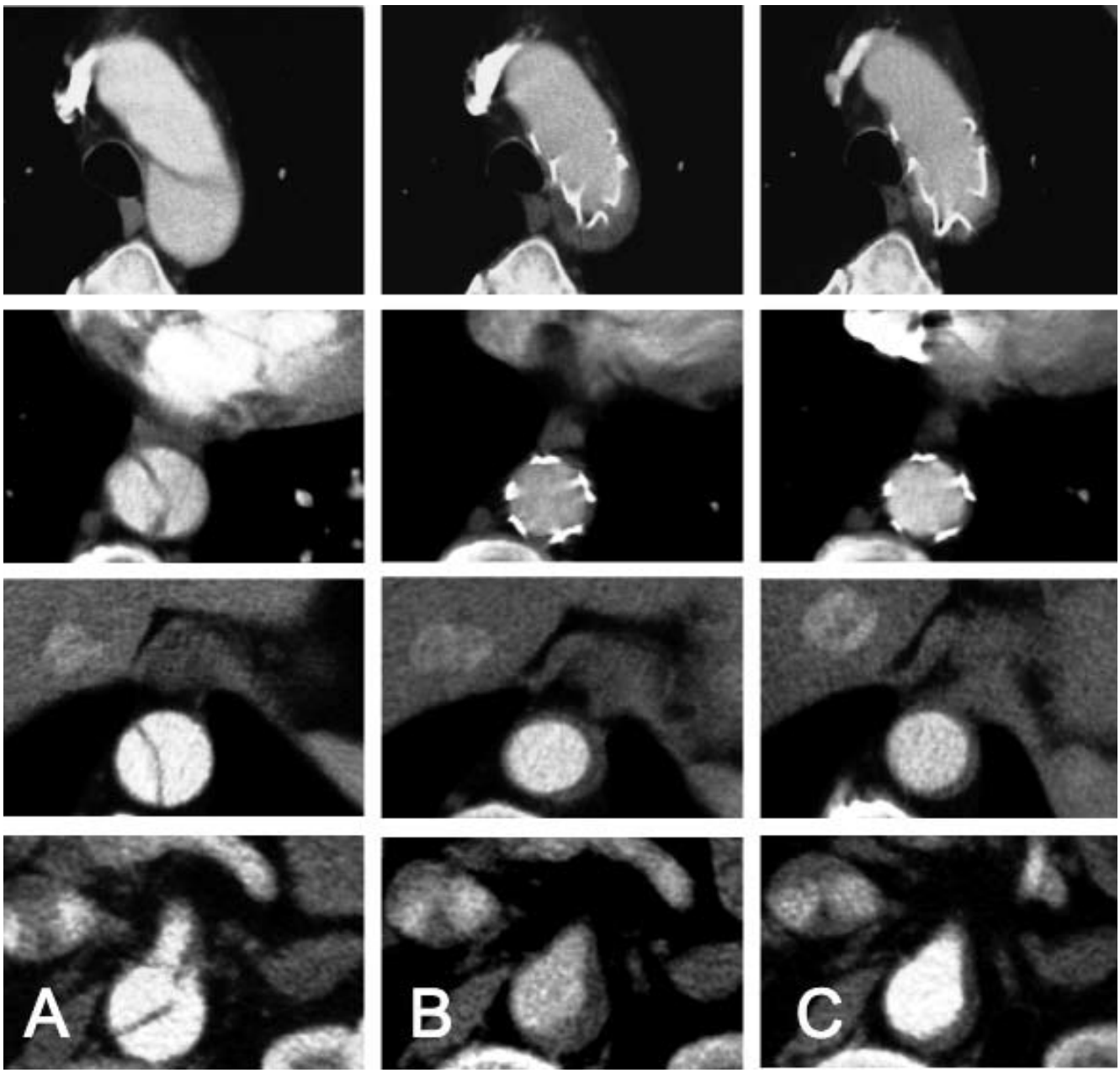

Figure 3. Stent-graft induced aortic remodelling in acute type B dissection. Note the communications between the true and false lumen at the thoracic and abdominal level (A). After stent-graft placement across the proximal thoracic entry, the entire aorta including the abdominal segment is reconstructed (B). With time "healing" of the dissected aortic wall occurs by means of progressive shrinkage of the thrombosed false lumen (C).

and the descending aorta is feasible (Figure 5) (46). This demanding and time consuming approach requires the skills of both cardiac and endovascular surgeons and intraoperative fluoroscopy, but lacks the precision of a staged procedure (47). Moreover, there is some resistance to one-stage endoluminal grafting in acute type A dissection as physicians are aware of fragile tissue and friable dissecting lamella likely to be injured or perforated by antegrade positioning of a stent-graft under non-circulating conditions. At present there are no endografts designed especially for use in the ascending aorta, nor for correcting dissections. Such challenges will certainly be addressed by customized stent-graft technology in the near future. Nevertheless, the concept of one-step hybrid repair with an antegrade stent-graft delivery might become part of the therapeutic armamentarium for complex type A dissections with life-threatening distal malperfusion, while a staged repair with retrograde stent-delivery appears to be a better option in stable situations (Figure 6).

ENDOLUMINAL TREATMENT FOR DESCENDING THORACIC ANEURYSMS

Degenerative aneurysms may involve one or more thoracic aortic segments and are classified accordingly. Sixty percent of thoracic aneurysms affect the ascending aorta, 40% are exclusively confined to the descending aorta, while another 10% involve the arch or extent into abdominal segments, respectively. Aetiology, natural history and treat-

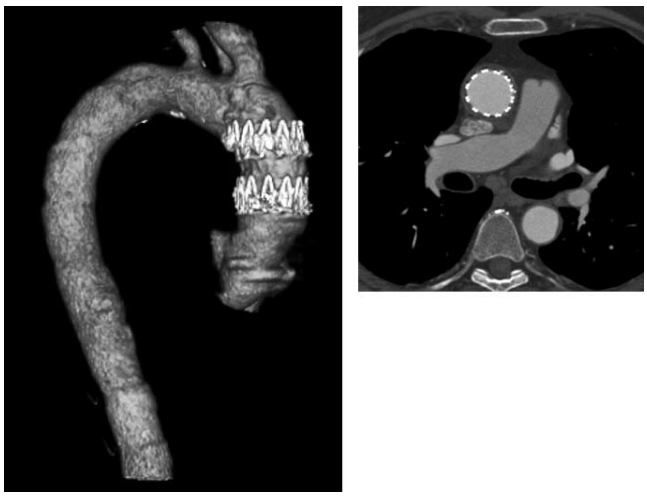

Figure 4. Nonsurgical exclusion of a localized tear in the ascending aorta. A short customized endograft was retrogradly advanced from the femoral artery to cover the entry of the lesion.

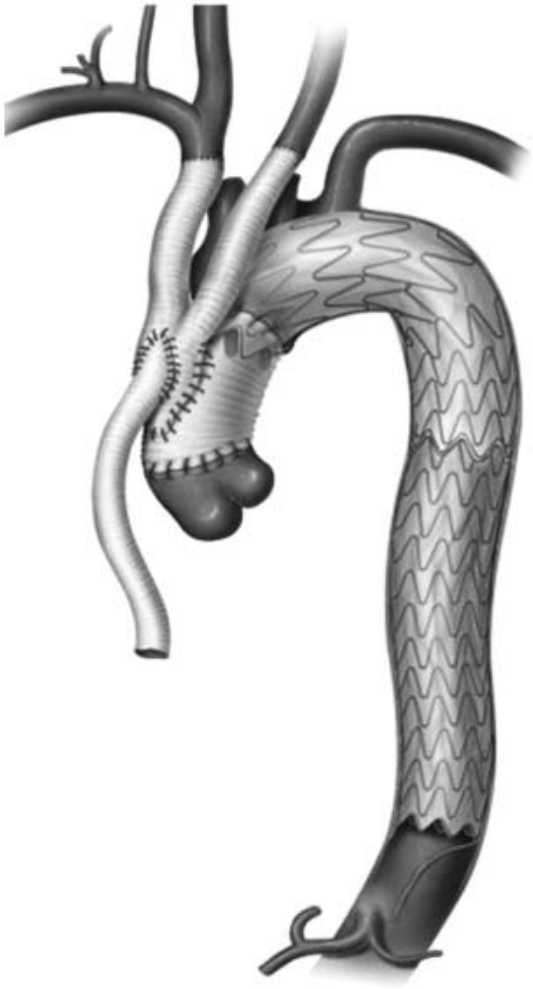

Figure 5. Illustration of single-stage repair in acute type A dissection combining an open ascending tube graft with simultaneous great vessel transposition and antegrade deployment of an endoluminal graft across the arch and the descending thoracic aorta.

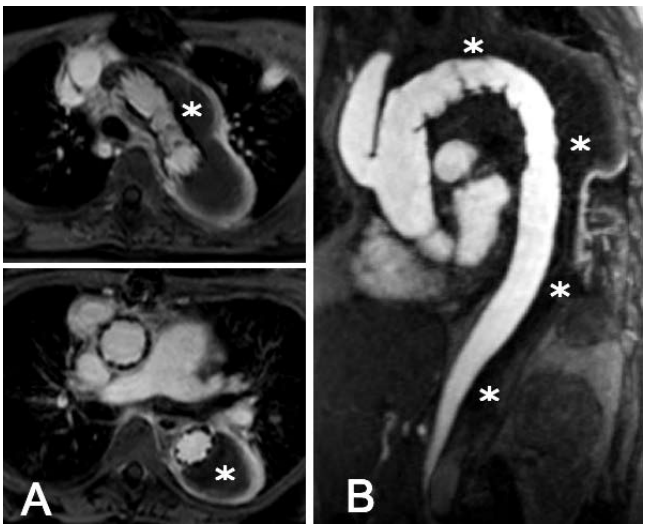

Figure 6. Staged hybrid approach for type A dissection with initial open ascending tube graft insertion and simultaneous head vessel debranching. At second stage, the distal false lumen was excluded by means of transfemoral stent-graft deployment across the aortic arch.

ment options differ for each of these segments (48). Observational studies revealed an average expansion of 0.1 cm per year; however, the growth-rate was higher in aneurysms affecting the descending rather than ascending aorta and was accelerated in Marfan-patients. For aneurysms exceeding 6 cm in diameter, the individual risk appears to rise to an annual rupture rate of 7% (49). In this scenario, endovascular stent-graft exclusion offers a promising therapeutic alternative with the advantage of a nonsurgical procedure potentially lowering postoperative morbidity and mortality (Figure 7) (4, 50-52). Recently, European multicenter-registries reported primary technical success in 80-90% of cases treated endoluminally for descending thoracic aneurysm (8,9). Major procedure-related neurological complications - including stroke and spinal cord ischemia - occurred in up to 8%. However, compared with standard open surgical repair, endovascular treatment appears to halve perioperative mortality with similar late survival and almost identical rates of reinterventions and ischemic spinal cord complications (53, 54). Patients considered suitable for stent-graft placement should have a proximal and distal segment of relatively normal aorta for fixation with satisfactory seal. These regions are often referred to as “landing zones” or “aortic neck” and should ideally encompass more than 20 mm free of aortic wall atheroma or thrombus. Close proximity to the arch vessels may complicate endografting for thoracic aortic aneurysm, necessitating intentional coverage of the left subclavian artery or even prophylactic bypass-surgery in selected cases (55, 56). At present, endovascular therapy is best reserved for those individuals with a suitable anatomy or poor surgical candidates (57). Technical refinements and miniaturization of the devices are required before routinely used for any aneurysm.

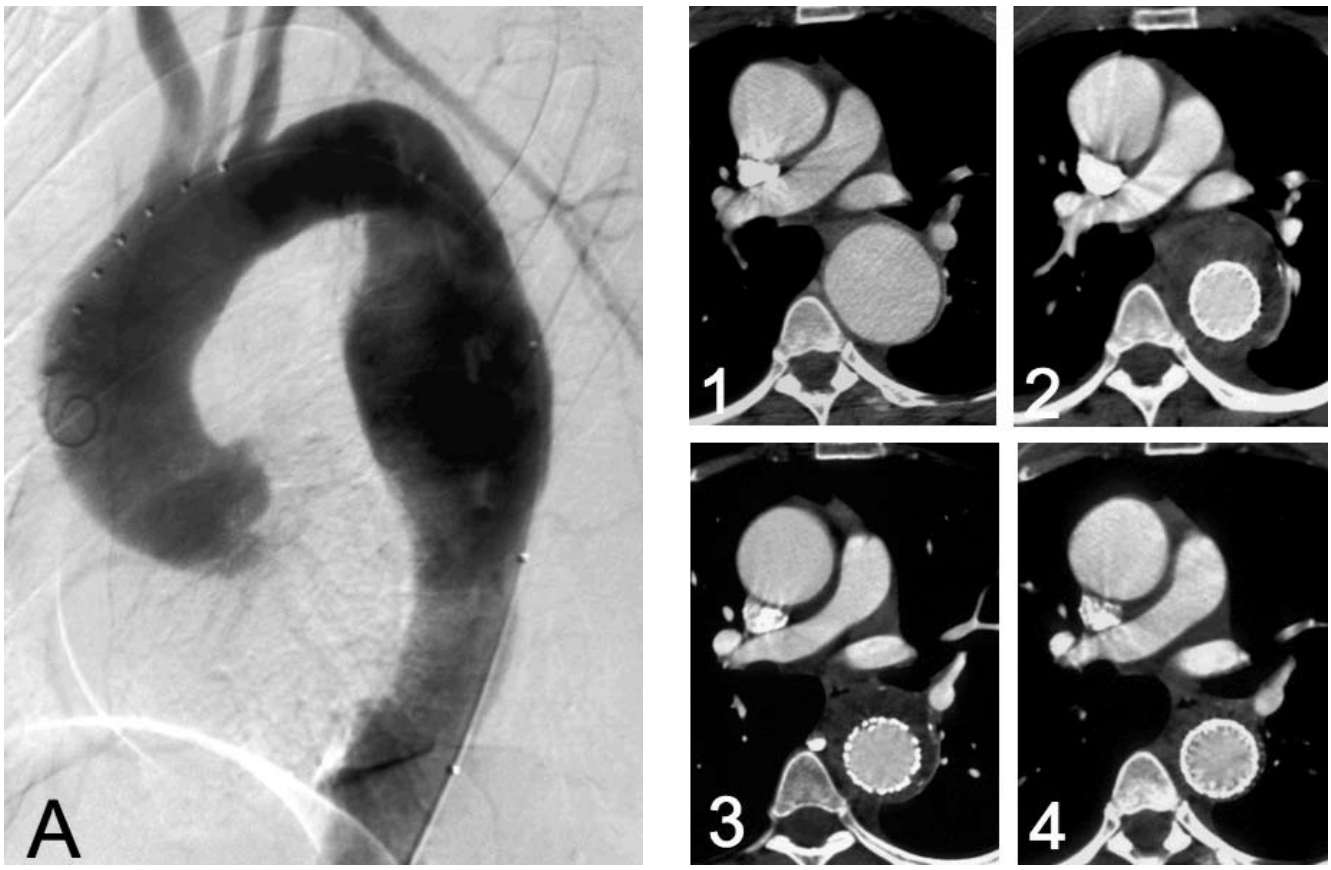

Figure 7. Preoperative angiography in a 52 year-old man with a thoracic aortic descending aneurysm (A). Computed tomography scans after successful stent-graft exclusion of the aneurysm demonstrate continued shrinkage of the periprothetic thrombus mass (1-4).

ENDOVASCULAR OPTIONS FOR INTRAMURAL HAEMATOMA

Approximately 5% of patients admitted to the hospital with suspected acute aortic dissection will be diagnosed as intramural haematoma (IMH) (58-60). IMH is characterized by haematoma formation between medial layers of the aortic wall without an associated intimal tear probably caused by spontaneous rupture of the aortic vasa vasorum with propagation of subintimal hemorrhage (61, 62). Compared with classic aortic dissection, intramural haematoma is observed more often in descending rather than ascending segments and predominantly occur in elderly patients (63). Malperfusion and pulse deficits are rare, although progression to frank aortic dissection occurs in 16 to 36%. Recently, observational studies demonstrated that a normal aortic diameter in the acute phase is the best predictor of survival with regression to normal morphology in one third of patients (64, 65). In a prospective study of 68 consecutive patients with intramural haematoma (12 type A, 56 type B) a maximum diameter over 50 mm and ascending aorta involvement were both predictive of early mortality (66). Similar to classic aortic dissection, early surgical graft repair should be standard treatment of IMH in the ascending aorta. Conversely, asymptomatic patients with involvement of the descending aorta can be monitored closely while on medical treatment (67), with endovascular intervention reserved for patients who develop complications such as persistent pain, penetrating atherosclerotic ulcer, signs of impending rupture or enlarging aortic diameter (17). Nonsurgical strategies such as endovascular placement of stent-grafts to cover the intramural haematoma have recently been associated with a 30-day mortality ranging from 0% to 16% and thus compare favourably with open surgical repair. On aggregate, IMH in the descending aorta per se is no reason for stent-grafting; however, in cases with progressive complications originating from IMH, endovascular strategies may be considered ranging from entry closure in dissection to exclusion of a local aneurysm or penetrating ulcer.

ENDOGRAFT MANAGEMENT OF PENETRATING ULCER AND PSEUDOANEURYSM FORMATION

The term “penetrating atherosclerotic ulcer” (PAU) describes a condition in which ulceration of an atherosclerotic plaque penetrates the internal elastic lamina and allows haematoma formation within media of the aortic wall (68,69). PAUs are most frequently located in descending thoracic aorta and in elderly patients with a history of hypertension, smoking and other atherosclerotic disease, e. g. pre-existing abdominal or thoracic aortic aneurysm. In one quarter of cases atherosclerotic ulcers may penetrate through the media to form saccular aortic pseudoaneurysm or less often perforate the adventia and cause transmural aortic rupture (40-43). The entity is associated with a variable amount of localized intramural haematoma, but may extend to classic aortic dissection in rare cases (70, 71). At present, no definite treatment strategy has been established for

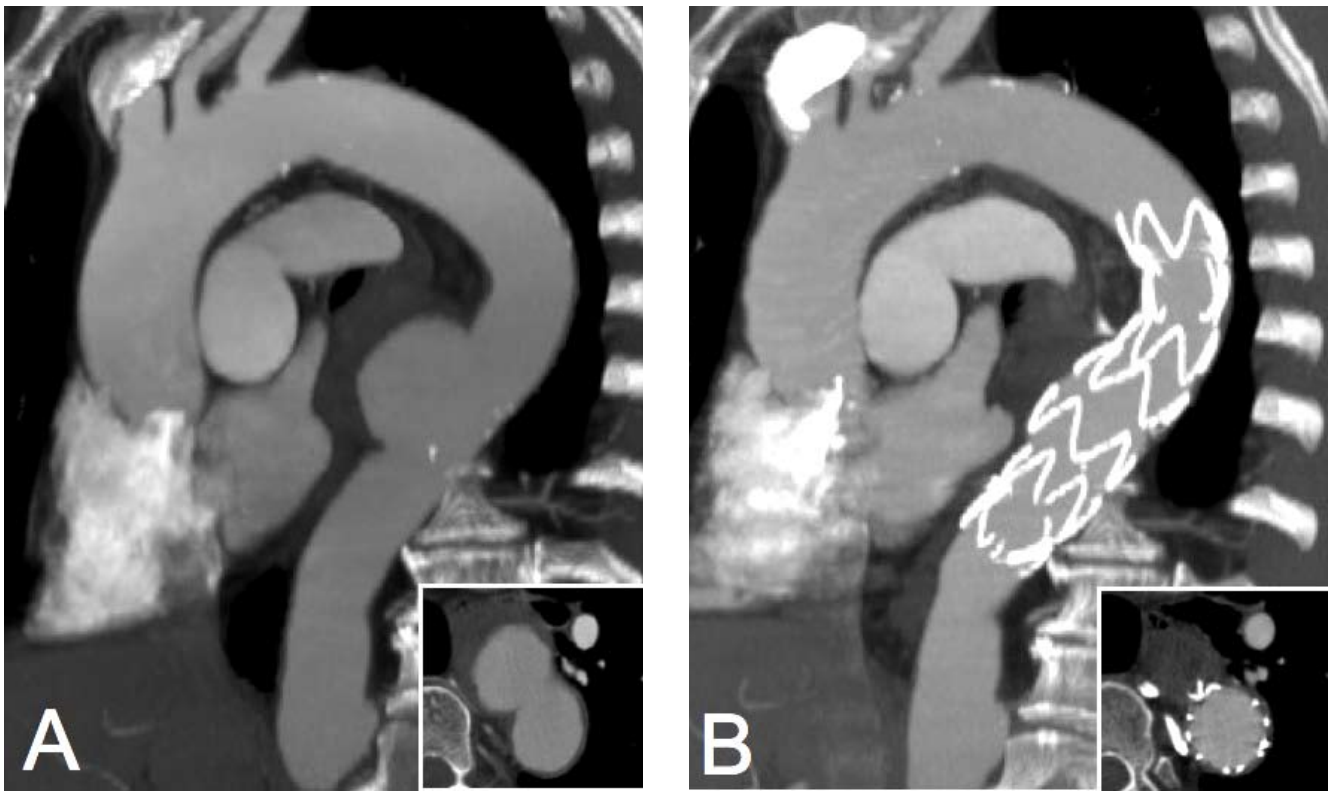

Figure 8. Penetrating aortic ulcer diagnosed in an elderly male presenting with acute chest pain (A). The patient was considered to be at high risk for rupture. Emergency application of a thoracic stent-graft enabled complete sealing of this limited aortic lanceration (B).

managing penetrating atherosclerotic ulcers. Certainly, unstable patients with evidence of contained rupture should undergo urgent repair. Continued or recurrent pain, distal embolization and progressive dilatation are also indications for surgery. However, it remains unclear if stable patients with PAU should undergo surgery or medical management (72). There is growing optimism that transluminal stent-graft placement may become an alternative to open surgery, as limited aortic disease constitutes an ideal condition for endovascular repair (Figure 8). Numerous case reports and smaller series confirm the short-term safety of stent-graft placement in symptomatic patients (73, 74), but long-term efficacy will require careful matching of endovascular repair to understand principles of patient selection and treatment modalities.

STENT-GRAFT REPAIR OF TRAUMATIC AORTIC TRANSSECTION

Traumatic aortic rupture commonly occurs as a consequence of rapid deceleration forces, including car and motorcycle collision, fall from height or blast injuries. It accounts for up to 20% of fatal motor vehicle accidents with prehospital mortality rates between 80 and 90% (75-77). The region subjected to the greatest strain is the isthmus, where the relatively mobile thoracic aorta joins the fixed arch at the site of the ligamentum arteriosum; aortic rupture occurs here in 90% of cases in clinical and pathological series (75, 78, 79). The lesion may be limited to the intima, but can potentially encompass all aortic layers forming medial laceration, false aneurysm and periaortic hemorrhage (78). In the vast majority of patients who survived the initial traumatic impact, affection of both the intimal and medial layer results in a localized outpouching of the diseased aortic wall. Despite advances in surgical techniques, mortality of emergent open repair exceeds 15% in current literature, depending on severity of associated traumatic lesions, preoperative shock and use of circulary assistance (77, 80, 81). A significant reduction of surgical mortality has been accomplished by deliberately delaying open repair in hemodynamically stable patients (82-84). Although this delayed approach is justified by objective data, it has to be taken into account that as many as 4% of patients awaiting surgery die due to aortic rupture within 1 week after traumatic injury (85). With the advent of stent-graft technology this less traumatic therapeutic approach attracts growing interests with no need for thoracotomy, aortic cross-clamping and cardiopulmonary bypass (86-88). As confirmed by serial imaging, restitution of aortic wall integrity can be achieved in almost all patients treated endoluminally, rendering stent-graft intervention an accepted first-line approach to traumatic aortic conditions (Figure 9). Recently, a comparative meta-analysis reviewed outcomes of 699 patients referred to endovascular or open repair after traumatic aortic transsections. With a technical success rate not different from open repair (96.5% vs. 98.5%, p=0.58), endovascular therapy was associated with lower periprocedural mortality (7.6% vs. 15.2%, P = 0.0076) and demonstrated an exceptional low incidence of paraplegia (0% vs. 5.6%, P < 0.0001) and stroke (0.85% vs. 5.3%, P = 0.0028) (89). Because most injuries occur at the aortic isthmus in younger patients the placement of a sometimes oversized and rigid device into an angulated aortic

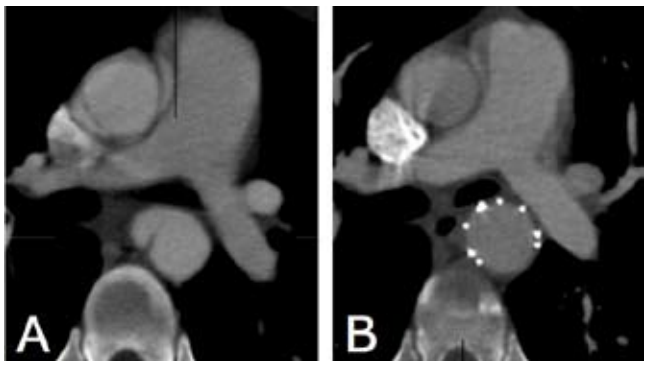

Figure 9. Traumatic aortic tear (arrow) diagnosed in a young man after motorcycle collision (A). The hemodynamically stable patient was elected for delayed endovascular repair 3 weeks after the initial traumatic impact. Note the complete attachment of the intimal lesion after stent-graft placement (B).

has raised concerns of iatrogenic injury and failing long-term durability. However, technology is improving and offers newer, more flexible and smaller devices. At present, standard thoracic stent-grafts are available, allowing their effective application in an emergency setting to prevent exsanguation from traumatic aortic rupture (80, 90-93).

ENDOVASCULAR MANAGEMENT OF AORTO-BRONCHIAL AND AORTOESOPHAGEAL FISTULAS

Aortobronchial fistulas (ABF) can be associated with a number of pathologic conditions of the descending thoracic aorta, including degenerative and dissecting aneurysms, para-anastomotic pseudoaneurysms secondary to previous open surgical repair, stent-graft erosion of the aortic wall, and mycotic aneurysms (94-96). Urgent intervention for this life-threatening disorder usually requires resection and graft interposition, but at the costs of high risk for death and paralysis, particularly in the setting of hemodynamically unstable patients. Even today, the operative mortality for traditional open repair of ABF using the clamp-and-sew technique reaches 20% (97). Since 1996 aortic stent-grafts have been increasingly used to manage ABF in patients who are at prohibitive risk for direct surgical repair. A recent meta-analysis demonstrated a cumulative 30-day mortality of only 8.3% with most of the cases reporting successful 1-year survival (98).

Aortoesophageal fistula (AEF) is another uncommon, but highly fatal condition, occurring most commonly in association with thoracic aortic aneurysms, foreign body ingestion, esophageal malignancy and traumatic aortic injury (99). Furthermore, secondary AEF is a well documented sequelae of prosthetic and endovascular repair of aneurysmal aortic disease. The widely accepted treatment modality for AEF is thoracotomy with aortic graft interposition, followed by surgical reconstruction of the oesophagus (100, 101). This procedure is associated with a high mortality and morbidity rate due to the poor clinical condition of patients at time of surgery. Aortic stent-graft placement for AEF has emerged as a less invasive therapeutic option for vascular repair in these high-risk patients (102). Today, this is confirmed by numerous case reports demonstrating efficacy to both control aortic bleeding and stabilize patients' condition before initiating further treatment (103-106). Despite promising short-term results it remains unclear whether endovascular aortic stenting in an potentially infected area can be seen as definitive treatment or serves as bridging maneuver to allow delayed aortic surgery in patients with aortobronchial or aortoesophageal fistulas.

PERCUTANEOUS ENDOVASCULAR REPAIR OF ANEURYSMS AFTER COARCTATION SURGERY

Coarctation of the aorta occurs in up to 5% of patients with congenital Heart, disease potentially leading to cerebrovascular morbidity, stroke and infarction, thus dramatically limiting life expectancy if left untreated (107). Open surgery used to be the standard of care and surgically treated aortic coarctation was initially considered successful and curative (108-110). It has been recognized, however, that late problems such as re-coarctation, aneurysm formation and potential rupture tend to occur within decades even after successful synthetic patchgraft repair or subclavian flap aortoplasty (111, 112). Today, aneurysms forming after previous coarctation surgery are amenable to endoluminal repair as the localized lesion is often accompanied by adequate landing zones ensuring perfect wall apposition of the stent-graft. Since open redo-surgery carries considerable risk, the endoluminal approach might emerge as the treatment of choice. Customized, tapered stent-grafts are now available from various manufactures to manage the potential discrepancies of proximal and distal "aortic neck" diameters in complex aortic lesions (Figure 10). Although preliminary series demonstrated a promising potential of endovascular stent-grafts to avoid thoracic redo-surgery (113-115), the durability of these devices is unproven as long-term results are not available yet.

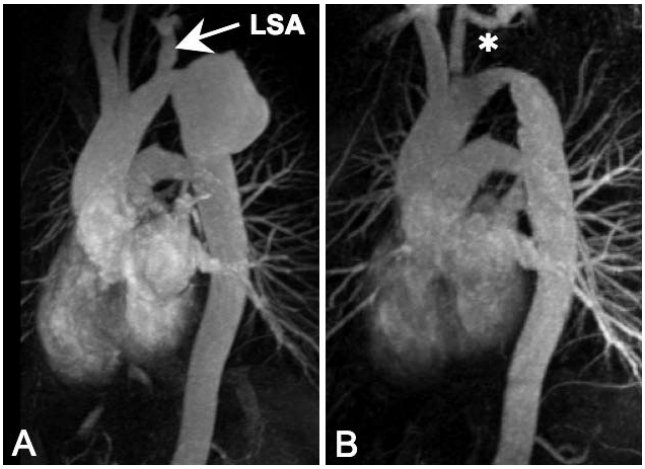

Figure 10. A patient presenting with large pseudoaneurysm 29 years after surgical correction of aortic coarctation (A). The aneurismal defect was excluded with a flexible third-generation endograft after previous transposition of the left subclavian artery (LSA). Narrowed aortic isthmus was left untreated as no significant pressure gradient was measured (B).

INTENTIONAL OCCLUSION OF THE LEFT SUBCLAVIAN ARTERY

Both technical and long-term success of endovascular strategies depend on anatomical conditions for optimal fixation of the endoprothesis, with landing zones ⩾2 cm in length. Close proximity between the left subclavian artery (LSA) origin and the degenerative aneurysm or primary entry tear is an important consideration. For this reason, complete coverage of the LSA ostium has to be used to expand the application of endovascular devices to aortic pathologies adjacent to the LSA. A recently published review article analyzed the need for subsequent transposition of the LSA in patients undergoing thoracic aortic stent-graft placement and found that only 4% exhibited early ischemic symptoms of the upper left extremity after intentional LSA occlusion. While 84% of patients were completely asymptomatic at follow-up, only 3% required elective left carotid-to-subclavian bypass due to weakness of the left arm (55). Thus, we do not favour routine prophylactic transposition or bypass-grafting of the LSA recommended by other groups (116-118). Our position is corroborated by the fact that most patients with an ultrasound-documented subclavian steal are asymptomatic (119). In addition, collateral perfusion of the left arm appears sufficient, as has been seen when antegrade flow of the LSA is sacrificed after surgery for aortic arch coarctation (120). Furthermore, auxiliary surgical revascularization procedures add to the overall risk of endovascular aortic reconstruction and should be reserved for patients with previous aortocoronary bypass surgery with use of the left internal mammary artery, critically stenosed or hypoplastic right vertebral artery, or a functionally compromised circle of Willis, or in presence of an anatomical variant, such as an aberrant subclavian (lusorian) artery. We recommend careful preinterventional screening of the supra-aortic arteries with combined use of Doppler ultrasound and 3D MRA to confirm the presence of normally sized, nonhypoplastic vertebral arteries and an appropriate anatomical connection to the basilar artery (121).

Extensive coverage of aortic segments has been reported to be a significant risk for spinal cord ischemia (122-126). Particularly, patients after repair of the abdominal aorta appear to be at risk because of interrupted spinal cord collateral blood supply secondary to ligation of lumbar arteries with previous open surgery (127-129). In those patients occlusion of the left subclavian artery without previous revascularization may contribute to an unpredictable risk of spinal cord ischemia as proximal collateral circulation, via the anterior spinal artery, a branch of the ipsilateral vertebral artery, is jeopardized. In summary, observational evidence suggests that intentional LSA occlusion may be justified when required for proximal anchoring of stent-graft in the absence of supra-aortic vascular pathologies and previous aortic repair (130).

HYBRID PROCEDURES FOR AORTIC ARCH PATHOLOGIES

The development of endovascular aortic surgery is characterized by the performance of increasingly complex procedures avoiding extended thoracotomy and extracorporeal circulation, (131, 132). The aortic arch morphology is challenging because of angulation and the proximity of the supra-aortic branches that need to be preserved. For traditional open arch reconstruction, using hypothermic cardiac arrest, extracorporeal circulation, and selective cerebral perfusion has been demonstrated to effectively assist in such major operations. However, open procedures for any arch pathology carry a high risk for in-hospital mortality (2-9%) and neurological complications (4-13%) (133-135). Therefore, classic surgery is often reserved for low-risk patients. As an alternative strategy, hybrid arch procedures (HAP) provide patient-centred solutions combining first stage debranching bypasses (to preserve cerebral perfusion) with a second stage endovascular exclusion of the affected arch. HAP is generally performed without hypothermic circulatory arrest or extracorporeal circulation, and may expand the treatment group to older patients with severe comorbidities or redo-surgery currently ineligible for open surgical intervention. There are two different hybrid approaches with either extra-anatomic or intrathoracic supra-aortic vessel transposition. To treat distal arch aneurysms involving both the left subclavian and the left common carotid artery, those vessels can be translocated upstream to the right common carotid artery approached via cervical access (hemiarch debranching) (136, 137). For arch aneurysms

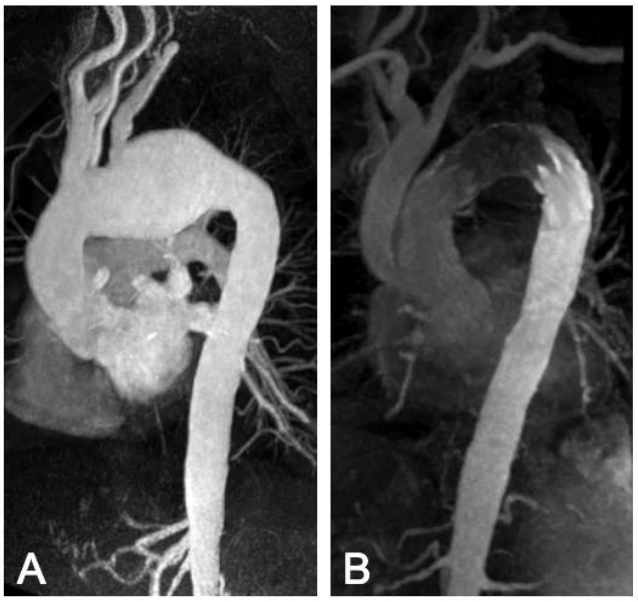

Figure 11. Aortic arch aneurysm in a 67 year-old man not eligible for classic surgical replacement. Hybrid approach included rerouting of the supraaortic branches with staged transfemoral implantation of an endovascular stent-graft across the aortic arch. Follow-up at 6 months revealed unimpaired bypasses and complete exclusion of the arch pathology (B).

extending to the innominate artery the ascending aorta can be used, via sternotomy, as a donor site for debranching bypasses (total arch debranching) and will serve as proximal landing zone for the endograft (Figure 11) (136, 139).

ENDOLUMINAL ELEPHANT TRUNK COMPLETION IN EXTENSIVE AORTIC DISEASE

Thoracic aortic aneurysms affecting the arch and proximal descending aorta continue to challenge physicians. Today, single-stage operations have been widely replaced by a the 2-stage approach with initial placement of an elephant trunk under hypothermic circulary arrest followed by a second stage procedure for surgical extension of the graft to the distal aorta (140). Mortality rates of 4-6% for the second-stage procedure were recently reported (141-143). Retrograde application of endovascular stent-grafts via femoral approach to complete the proximal procedure avoids the requisite thoracotomy and may improve the morbidity and mortality of the patient population at risk. In a recently published series of 22 patients Greenberg et colleagues could demonstrate that mortality as well as neurological complications surrounding the endovascular procedure were exceptionally low, thus allowing safe performance of endovascular completion of elephant trunk repairs (144). Given the complex aortic morphology, it is beneficial to have access to tapered prostheses with active fixation systems, which allow accommodating disparate proximal and distal diameters, and similarly reducing the risk for caudal migration from pulsatile forces. The elephant trunk graft in general provides an adequate overlap for stent-graft insertion of at least 4 cm (144). However, excessive length and tortuosity of the elephant trunk graft can make the endovascular portion of the repair much more complicated and possibly less durable. Obviously, delaying the second-stage procedure will increase the risk of rupture, and thus, all efforts should be made to streamline the recovery from the first stage and complete the second stage expeditiously. Improvements in implant design and delivery systems will further simplify the second-stage portion of these complex aneurysm repairs. Endovascular elephant trunk completion may drastically diminish the complication rate in extended aortic repair, but is still in need of long-term results.

CONCLUSION AND FUTURE DIRECTIONS

The emerge of endovascular strategies as an alternative to open surgery constitutes an exciting field in patient care. Although it is apparent that high-risk patients will benefit from this technology, the exact role of stent-grafting remains to be defined as we continue to accumulate long-term data and as devices and techniques evolve. Instead of replacing conventional surgical treatment, endovascular repair will likely play a complementary role and offer a less invasive option in our treatment armamentarium. It is clear that limitations of both approaches are subject to change and the risk for open surgery somewhat subjective (judgement of comorbidities and physiological reserve), whereas contraindications for endovascular treatment are mainly defined by anatomical constraints. Current limitations of nonsurgical reconstruction will be addressed with new designs of highly individualized low-profile devices in order to expand applicability of stent-graft technology in the thoracic aorta. Interestingly, for both open and endovascular techniques in many scenarios the answer to the ethical question of justification of treatment is not in yet, because prospective data from randomized studies are not available nor are standard operational procedures or guidelines. However, if one insists on strict proof (or strict disproof) in empiric science, one will never benefit from experience and never learn from it how wrong one has been. Nevertheless, even in a world of rapidly advancing technology, it is ironically still wise to remember old principles of responsible use of clinical judgment and experience for the benefit of our patients. The growing segment of older patients with multiorgan comorbidities deserves a holistic approach, the intelligent use of prognosticating tools, and close interdisciplinary cooperation in a medicoethical framework.

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Technical Aspects of Subintimal Angioplasty of the Crural Arteries

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Abbreviations and Acronyms:
SA — subintimal angioplasty;
ATA — anterior tibial artery;
PTA — posterior tibial artery;
FA — fibular artery.

INTRODUCTION

Recent years are marked by a significantly growth of the interest for endovascular methods of revascularization in various forms of lower extremities ischemia, including searching for effective, minimally invasive and inexpensive methods of blood flow restoration in patients with chronic critical ischemia. Occlusion of the crural arteries, which is quite commonly observed in such patients, is the most challenging aspect of revascularization. Subintimal angioplasty (SA) technique was suggested as a method for arterial patency restoration in extended chronic occlusions. A. Bolia et al. (1990) (1) reported the results of treatment of 71 patients with occlusions involving the femoropopliteal segment.

The method described by the authors, which is currently accepted as a classical, involves intentional advancement of the loop-shaped hydrophilic angiography guidewire into the subintimal space near the proximal edge of occlusion using a catheter. Then the catheter-guide complex is advanced subintimally until spontaneous reentry into the true artery lumen distally to the occlusion site is achieved. Then balloon dilatation is performed for creating of subintimal channel exteriorly of the lumen, and through this channel antegrade blood flow is established. In contrast to intraluminal angioplasty, when the reconstructed artery lumen is surrounded with atherotrombotic masses, subintimal channel is relatively smooth and blood is not in contact with atheromatous masses.

The technical success was relatively high (76%), and the complication rate was low (5.6%). At 6 months after successful SA, the clinical success was maintained in 84% of patients. Later these and other authors began to use SA of the crucial arteries in CLI (Critical Leg Ischemia) patients (2, 3). Several years later, a number of centers reported promising long-term results obtained with this technique use, which were similar to results of bypass surgery (4,5). Minimal invasiveness, low cost and high effectiveness of SA caused natural enthusiasm of medical community. However, despite the theoretical appeal and seeming simplicity of the method, it is not widely used. At present, SA of the crural arteries is used routinely only in a limited number of medical centers, mostly in Europe.

The technical success of SA of the crural arteries varies from 74% to 92% (3, 4, 6). However, these data show only the percentage of legs in which blood flow to the foot was restored at least in one crural artery, despite SA might be used in all three. Analysis of difficulties occurring with the use of standard technique of SA of the crural arteries and causes of its failure, is practically absent, that is far from helping for further wide-spreading of this method.

The purpose of this work was to investigate the factors affecting the technical success of SA of the crural arteries, and to analyze difficulties and failures occurring with its usage.

MATERIAL AND METHODS OF THE STUDY

We have performed the retrospective analysis of angiograms and reviewed the reports on performed endovascular procedures, in which SA of at least one from three crural arteries was performed.

Materials of the study consisted of the procedures of peripheral angioplasty aimed to revascularization performed on 54 legs in 51 patients with chronic critical ischemia in the period from February 2005 till December 2009. SA was attempted for blood flow restoration in 66 crural arteries. The indication for SA was extended (more than 5 cm) occlusions of type D according to TASC- 2000 classification. The length of occlusions ranged from 5 cm to 24 cm, making on average 17.5±7.3 cm. Patients were aged from 46 to 89 (mean age 79.5±6.5 years). Sixty two percent of patients suffered from diabetes mellitus. In 46 (85%) observations arterial lesion was of multilevel nature, and revascularization via SA or transluminal angioplasty was performed in the femoropopliteal segment as well.

When assessing angiograms and reports on performed interventions we noted technical failures and complications of the standard technique of SA occurring at each of its three stages: initiation of dissection, advancing of guidewire-catheter complex

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along the occlusion, entering the true lumen. Further the methods used for coping with occurring difficulties were reviewed and assessed for their efficacy.

SUBINTIMAL ANGIOPLASTY OF THE CRURAL ARTERIES

All patients were given a combination therapy of clopidogrel and aspirin according to the coronary stenting protocol. In case of procedure successes intake of clopidogrel for at least one month and lifelong intake of aspirin were recommended. All interventions were performed under local infiltration anesthesia at the site of artery catheterization. Additional epidural anesthesia was performed in14 patients who were unable to maintain their leg in horizontal position due to ischemia pain in rest. The presence of a patent artery segment at the level of the ankle and/or in the foot on angiography was considered to be an anatomical criterion for the feasibility of SA.

Subintimal recanalization and angioplasty of the crural arteries were performed using standard technique as follows: In all cases arterial access was performed via antegrade puncture of the common femoral artery. 5F and 6F introducers were used for catheterization depending on profiles of the used tools. In case of occlusions in the femoropopliteal segment intraluminal or subintimal recanalization and angioplasty were performed. A 0.035 inch diagnostic hydrophilic guidewire (Terumo, Japan) was looped in the lumen of patent segment of occluded crural artery or in the lumen of the popliteal arteria using 4F or 5F vertebral angiographic catheter. A guidewire was advanced to the border of occlusion using a catheter under X-ray guidance, and dissection was initiated by advancing the loop. As a rule, the loop entered the subintimal space without difficulties. The specific sign of subintimal placement of guidewire was the diameter of the loop exceeding that of the artery lumen. Further, the guidewire-catheter complex was advanced along the occlusion. Then, the entrance into the true lumen, so-called "reentry", occurred at the end of occlusion. The hydrophilic guidewire was replaced with a guidewire of 0.018 inch in diameter, and balloon dilatation of subintimal tract was performed using balloon catheters (2.5 or 3 mm in diameter and 80-150 mm in length) from different manufacturers. In case of > 30% residual stenoses revealed by control angiography, balloon dilatation was performed again. During the procedure 5000 7500 IU of unfractionated heparin was administered intraarterially. If necessary, 0.2 mg nitroglycerine was administered intraarterially to eliminate a spasm.

In case of technical difficulties occurring during the above stages of standard SA technique, additional technical approaches, listed in Table 1 were used.

EVALUATION OF THE RESULTS OF SA USAGE

The standard SA technique was considered to be technically successful in case it allowed to perform all stages and to restore blood flow without use of additional techniques. Observations in which the used additional techniques was required for successful SA were considered to be a success with technical difficulties. Cases in which SA failed were considered to be a technical failure.

The method-specific negative consequences of SA usage requiring special treatment or worsening the hemodynamic state of the leg were considered to be SA complications.

RESULTS

Technical results of SA of the crural arteries are provided in Table 2. The standard SA technique was successful in 22 (33.3%) arteries only, and various technical difficulties occurred in 44 cases. Application of additional techniques allowed for successful completion of SA procedure in other 30 arteries. The number of cases when different techniques were used and their effectiveness are provided in Table 1. In total, patency was successfully restored in 52 arteries (78.8%).

Impossibility of spontaneous reentry was the most common technical problem observed with SA of 17 (26%) crural arteries. Perforation of the artery by loop of guidewire was noted in 6 (9%) cases only, but in 3 out of them the perforation led to procedure failure.

According to our definition, SA technique-related complications occurred in 5 cases (7.6%). In one

Table 1. Technical approaches used for to overcome the difficulties met with SA.

SA stage	Technical problems	Technical approaches	How many times it was used/success (%)
1	Impossibility to initiate the dissection due to the absence of a patent proximal arterial segment	Retrograde catheterization of the patent segment at the ankle level and performance of a retrograde SA	8/6 (75%)
	Impossibility to enter the patent proximal arterial segment with a guidewire loop due to its stenosis	Dilatation of a patent segment with subsequent loop formation inside it	6/6 (100%)
2	Impossibility of loop advancement because of insufficient support	The use of an inflated balloon catheter of 3 mm diameter for the support of a 0,035 hydrophilic guidewire	12/9 (75%)
	Arterial perforation with the guidewire loop	The guidewire loop was withdrawn above the perforation and an attempt to direct it along another arterial wall with a catheter was made	6/3 (50%)
3	The loop is the plane of an already patent arterial segment, but spontaneous reentry does not occur	The loop was removed and angiography was performed. In case of a true lumen detection we tried to pass it with a 0,018 inches guidewire. If no lumen was seen, we tried to perform the reentry with a rigid hydrophilic coronary guidewire of the type Pilot 150 or 250 (Guidant, USA)	17/11 (65%)

Таблица 2. Результаты применения СА артерий голени.

Показатель	ПББА	ЗББА	МБА	Всего	%
Успешная стандартная СА	10	8	4	22	33,3
Успешная СА с техническими трудностями	15	8	7	30	45,5
Неудача СА	8	2	4	14	21,2
Всего	33	18	15	66	100

Обозначения:
ПББА – передняя большеберцовая артерия
ЗББА – задняя большеберцовая артерия
МБА – малоберцовая артерия

case perforation in the middle third of the anterior tibial artery was accompanied with marked extravasation requiring coil embolization of the artery to avoid development of compartment syndrome in the anterior muscular bed of the crus. In 4 cases, closure of large collaterals due to absence of spontaneous reentry and failure of additional techniques was noted. These have no clinical consequences, since an antegrade blood flow to foot was successfully restored through other crural arteries.

DISCUSSION

Obtained data show that SA of the crural arteries is an effective revascularization method, but technical difficulties with the use of this method occur quite frequently. This situation is explained in a great extent by the fact that in our study and in works of other authors, SA of the crural arteries was performed only in patients with critical ischemia. The morphology of arterial lesion in such patients is rarely characterized by relatively unchanged arterial segments above and below of occlusion, which is an ideal condition for SA. Significant proportion of patients with diabetes mellitus makes the procedure even more complicated as quite often they need the restoration of patency in certain crural artery supplying the area of tissue defect regardless to morphology of its lesion.

The most common technical problem in our study was the absence of spontaneous reentry, which was seen in every fourth case. In our opinion, it was related to marked changes in the patent segment of the artery distal to the occlusion, which is commonly observed in diabetes mellitus. A loop of hydrophilic guidewire of 0.035 inch in diameter cannot enter into the very narrow lumen of the artery. The attempts to achieve a spontaneous reentry by prolongation of dissection generally fail, but sometimes lead to the closure of collaterals, through which the distal parts of arteries are perfused (7). This occurred in 4 of our cases. Some authors report that prolongation of dissection into the patent segment can preclude performing of distal anastomosis and bypass surgery in case of failed endovascular revascularization (8). In order to avoid these adverse events we made it a rule not to advance the loop more than for 1 cm in the plane of distal patent segment. If no reentry was reached, the loop was withdrawn and the above techniques were used with the efficacy of 65%.

We believe that the most difficult problem with the use of SA of the crural arteries is the impossibility to perform an antegrade subintimal recanalization. A retrograde SA requires catheterization of patent artery segment at the level of the ankle. In our study, this technique was necessary only in case of complete absence of proximal patent artery segment, however, in other authors' works the main indication for this technique usage was the impossibility to reach reentry (9). Due to anatomical reasons, the absence of patent segment, which is required for SA start, is equally seen in ATA and PTA, which originate at an angle from the popliteal and tibioperoneal arteries, respectively. Solving this problem requires catheterization of patent artery segment at the level of ankle and performance of retrograde SA. To illustrate this technique, a clinical case report (from material of this study) is provided on Figures 1A, B and C. Artery perforation require embolization in this case only, and in other cases it has no notable consequences. The "benign" nature of this complication in the crural arteries was noted by other authors as well.

Taking into consideration the multilevel nature of occlusion in patients with critical ischemia, the revascularization of the crural arteries is often combined with revascularization of other arterial segments, and with other endovascular methods as well. The choice of revascularization method depends only on the morphology of arterial lesion and available resources. No stenting was performed in any case of SA of the crural arteries. It is worth noting that, in general, SA is a very useful tool in the repertoire of endovascular surgeon, as it allows restoring patency of extended chronic occlusions with least expenses.

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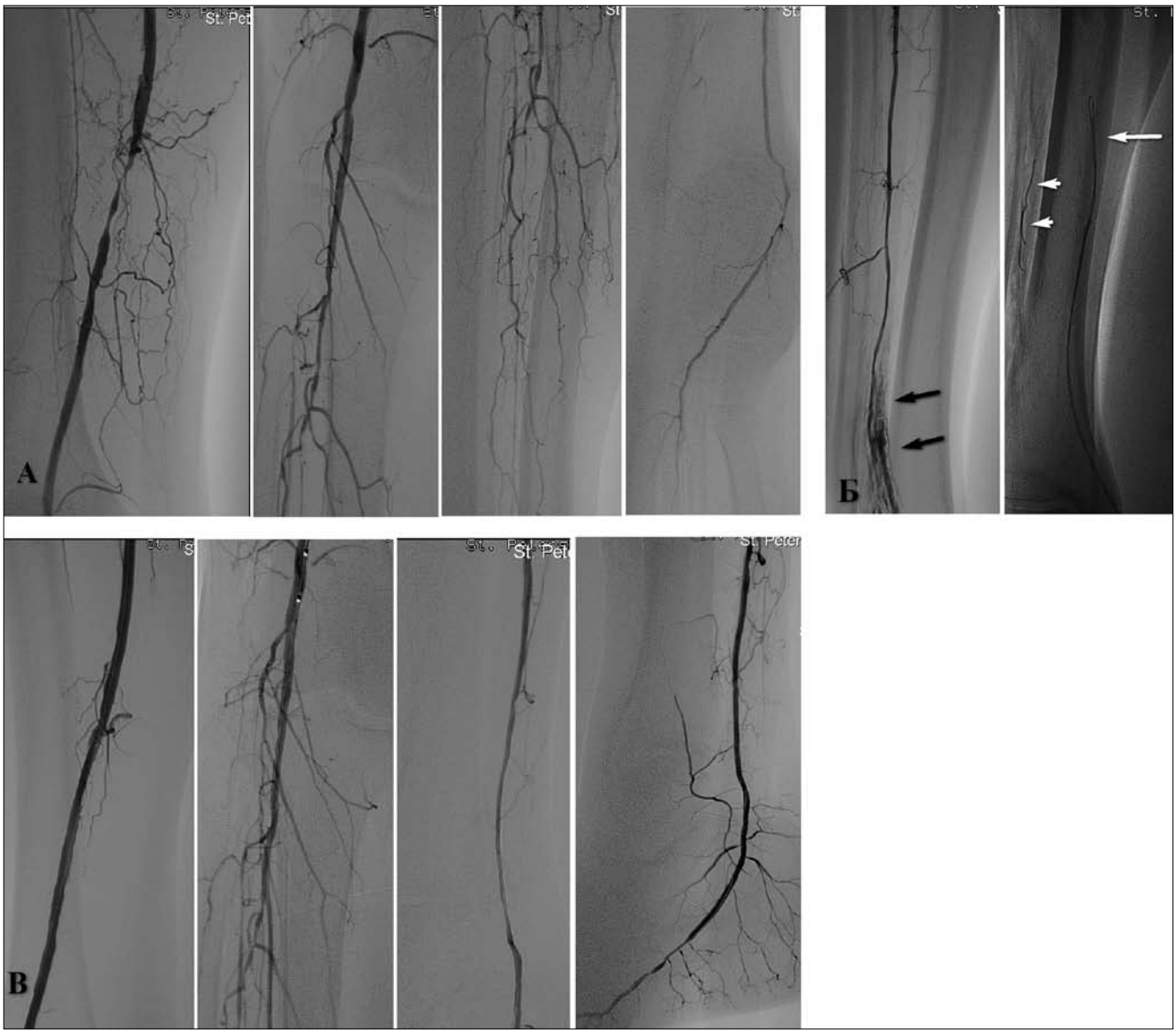

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"Kissing" Stent Technique to Treat Stenoses in Adjacent Renal Arteries

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Key Words: renal artery stenosis, kissing, stent, and bifurcation.

INTRODUCTION

Renal artery stenosis is the most common cause of secondary hypertension, noted in nearly 5 % of hypertensive patients (1). Atherosclerotic lesions are predominantly located at the ostium of the renal artery, within 2 to 5 mm from the aorta (2). Stent placement compared to balloon angioplasty has been shown to improve immediate and long term outcome by preventing immediate elastic recoil due to extensive atherosclerotic plaque (3-6). Occasionally, an accessory renal artery is present in addition to the main artery. These arteries can have separate ostia in close proximity or a common ostium with a very proximal bifurcation. Revascularization of lesions in renal arteries with such anatomy without jeopardizing the integrity of either branch, can be technically difficult (7).

CASE PRESENTATION

We report the case of a 59 year old female with poorly controlled hypertension despite multiple medications, multivessel coronary artery disease, chronic kidney disease stage III, and bilateral renal artery stenosis. A renal Doppler ultrasound revealed significant (> 70%) bilateral renal artery stenosis. Her right and left kidney were 10.2 cm and 9.8 cm in length respectively. Diagnostic angiography revealed a solitary right renal artery with a 90% stenotic ostial lesion and two equally sized left renal arteries with 90% stenotic ostial lesions and origins in close proximity from the aorta (Fig 1A). The baseline serum creatinine was 1.4 mg/dl with a creatinine clearance of 55 ml/minute.

An 8FR 11cm sheath (Boston Scientific, Inc., Natick, MA, USA) was inserted into the right femoral artery. An 8FR Veripath renal double curve (RDC) Peripheral Guiding Catheter (Abbott Vascular, Santa Clara, CA, USA) was telescoped close to the renal arteries over a 6FR diagnostic internal mammary artery (IMA) catheter (Cordis, Miami Lakes, FL, USA) after a 0.014 in. Spartacore guidewire (Abbott, Santa Clara, CA, USA) had been advanced into the lower renal artery. The 6FR IMA diagnostic catheter was removed. Baseline angiography was performed and the reference vessels sizes were obtained with on-line quantitative angiography. Another 0.014 in. Spartacore guidewire was inserted in the superior left renal artery. The guiding catheter was then advanced close to the ostia of the vessels. Two 3.0 X 15 mm Fire Star™ RX PTCA Balloons (Cordis, Miami Lakes, FL, USA) were positioned in a "kissing" technique and inflated to 8.0 atm. (Fig 1B). Due to a suboptimal angiographic result, a 4.0 X 12 mm RX Herculink Elite Renal Stent (Abbott, Santa Clara, CA, USA) was inserted in the ostium of the inferior branch and deployed at 10.0 atm. (Fig 1C). This stent was strategically placed with 1 to 2 mm protrusion into the aorta to assure adequate scaffolding of the ostial plaque. A 4.0 X 15 mm Express™ Renal Stent (Boston Scientific, Natick, MA, USA) targeted for the superior branch could not pass the struts of the inferior stent protruding into the aorta. A 5.0 X 12 mm VOYAGER™ RX Coronary Dilatation Catheter (Abbott, Santa Clara, CA, USA) was inserted and inflated at 6.0 atm in the inferior branch stent allowing the easy passage and placement of the stent at the ostium of the superior branch (Fig 1D). The superior branch stent was subsequently deployed and inflated to 10 atm. Subsequently, both stents were simultaneously dilated to 8 atm in a "kissing" fashion (Fig 1E). Post intervention angiography revealed an excellent result (Fig 1F).

This case could have been completed by several alternative approaches. The first alternative technique could have been to initially stent the superior branch then stent the inferior branch, possibly minimizing interaction with the proximal struts of a stent protruding into the aorta. A second option would have been to use two separate guiding catheters via bilateral common femoral artery accesses. A third approach would have been to use coronary balloons and stents via an 8 Fr sheath or guiding catheter thus taking advantage of their lower profile compared to peripheral stents. However, one potential disadvantage of using coronary stents in this application is the inferior radial strength which may make it difficult to defeat the vascular recoil of aorto-ostial renal plaque. Irrespective of the method employed, simultaneous balloon inflations in a "kissing" fashion are important to protect both vessels because of the proximity of their ostia.

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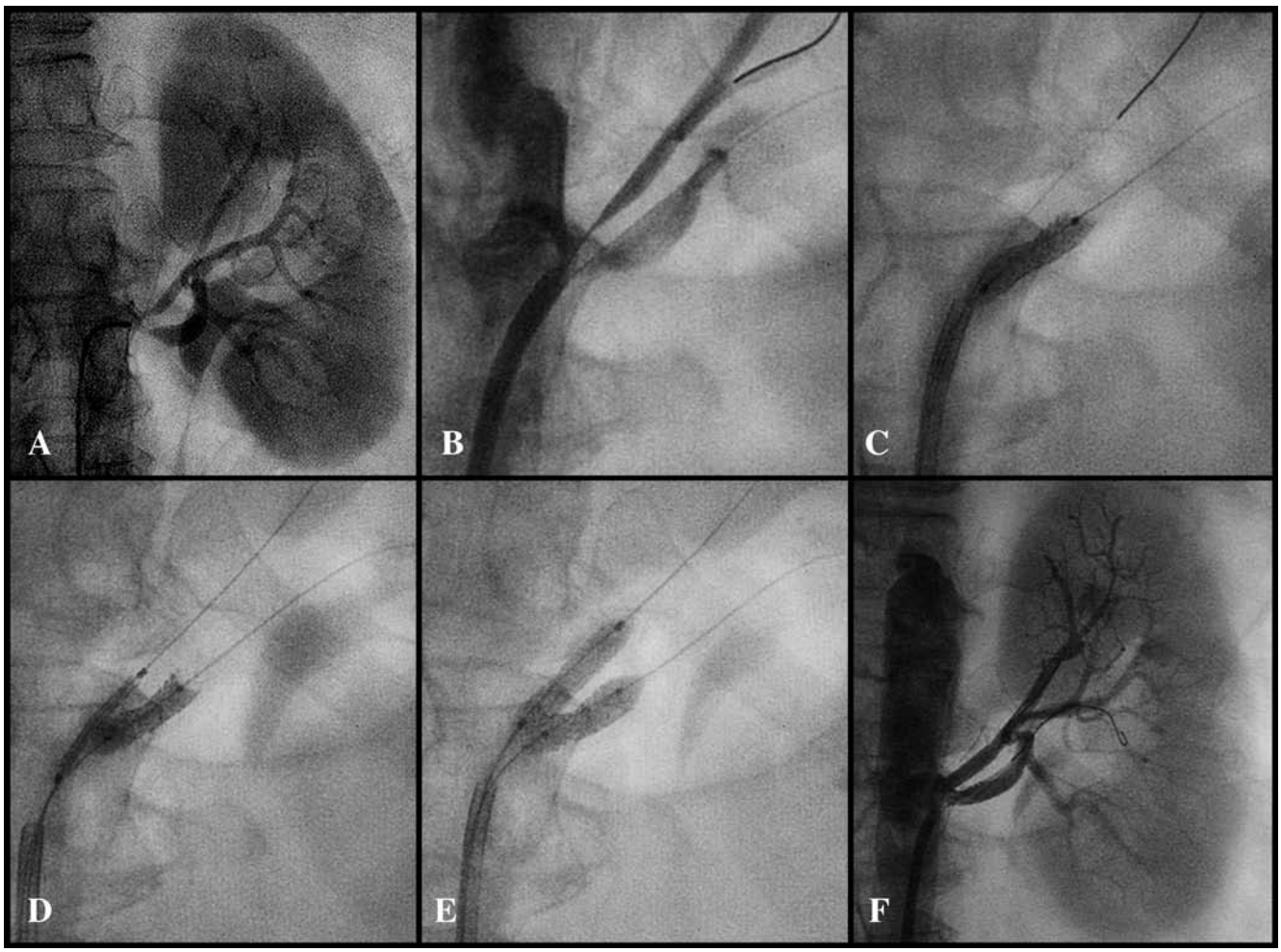

Figure 1. Baseline angiography of the left renal arteries (A), result after "kissing" balloons (B), deployment of lower artery stent (C), insertion of upper stent while balloon inflated in lower artery (D), "kissing" balloons in stents (E), and final result (F).

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Man's Normal Heart Right Atrium Ultrastructural Features

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INTRODUCTION

The detailed study of the right atrium (RA) subtle structure, three-dimensional organization of its elements and their interaction is urgently dictated by needs of clinical and experimental cardiology and cardiovascular surgery (15, 16, 20, 25, 26). The knowledge of the detailed RA ultrastructure is necessary both for understanding pathological processes touching it, and for exposure of local hemodynamic infringements. A number of cardiovascular interventions, aimed at hemodynamic or anatomic correction of various heart defects, especially congenital malformations, require intervention just on the RA. At that, the conditions of the RA functioning change compared to the initial. The data on microanatomy and microtopography of the RA allow to study the results of structural reorganization of its tissues in corrective interventions, and to adequately predict their reaction to changing intracardiac hemodynamics and microanatomy as a result of surgical or drug interventions. It is also important for the estimation of the new reconstructive operations results. Various interventions on the heart conducting system also require detailed data concerning spatial ultrastructure of the RA walls, especially their internal microrelief (4, 11, and 17). It is indisputable, that only scanning electron microscopy (SEM) enables to study the surface microrelief of various organs, tissues and separate cells, to receive the most realistic representation about spatial construction of the functioning structures.

The researches on spatial ultrastructure of human and animal heart with the help of the SEM have been carried out, since the 1970ies , when the present boom in this area was marked (5, 7, 8, and 10). Despite numerous researches on surface microrelief of various components of cardiovascular system, carried out during the last four decades, there is a set of blanks. The data of different authors, at times, are inconsistent and isolated, and the significant part of a researched material is submitted from the experimental animals (2, 6, 9, and 19). There are no the detailed data about normal spatial orientation of microrelief components of the various human RA parts. Despite numerous studies of the coronary system, the data concerning the vascularization of various parts of human RA are scarce (12, 13, 18, 21, 22, and 23).

Our research was aimed at the study of three-dimensional microanatomy and microvascular bed of various parts of the normal RA in humans using a combination of SEM and light microscopy techniques.

MATERIAL AND METHODS

We examined tissue from various sections of the RA of 18 individuals (10 male, 8 female) ages 25 to 45 who had perished from acute trauma. As judged by autopsy results, all these individuals were free from cardiovascular pathology of any kind. The hearts were obtained no later than 24 hours after biological death in the Republican Forensic Medicine Bureau with family consent. Resuscitation attempts were made in twelve cases, either in the ambulance or in hospital settings, but none for more than 45 minutes. The tissue was exposed to complex morphological study with the use of light and scanning electron microscopy. For the light microscopy study, the material was fixed in a 10% solution of formaldehyde in a 0.1 M phosphate-saline buffer with a pH of 7.4 for 1-3 days. After the material was flushed with the solution of phosphate-saline buffer and dehydrated in ethanol solutions of increasing concentration, the slices of tissue were placed in paraffin. Sections of 4 microns thickness were stained with hematoxylin and eosin. All histological preparations were examined and photographed using light microscopes Biolam, MBI -15 (LOMO PLC, Inc., St. Petersburg, Russia) and Axioskop-40 (Carl Zeiss, Inc., Oberkochen, Germany). After the heart was removed from the thoracic cavity, it was injected with a cold 2.5% solution of glutaraldehyde on 0.1 M of a phosphate buffer with a pH of 7.4. Then tissue was excised from various parts of RA and additionally fixed in the same fixative at a temperature of +4 C for 1 day. Following this, the samples of tissue were flushed in phosphate-saline buffer solution and fixed in 1% solution of osmium quadroxide, dehydrated in acetone solutions of increasing concentration and dried by a method of transition through the critical point of carbon dioxide with the use of HCP-2 device (Hitachi Medical Corp, Inc, Tokyo, Japan). The dried samples were mounted on aluminum carrying bases with electrically conducting glue. A thin layer of chemically pure gold was applied to the tissue surface using an ionization device (IB-3, Hitachi Medical Corp, Inc., Tokyo,

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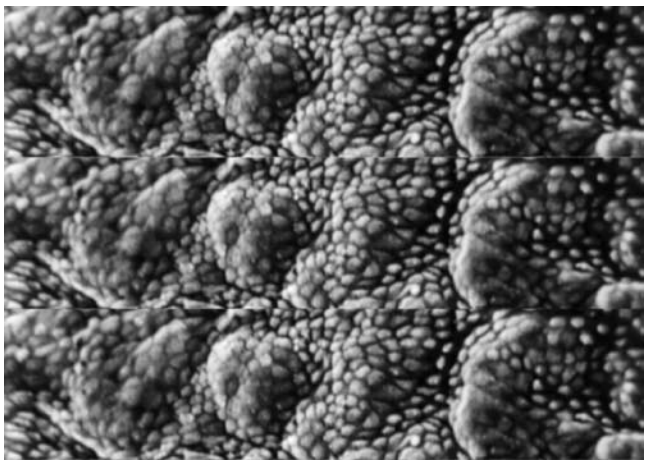

Figure 1. Epicardial surface of the RA. SEM x 200.

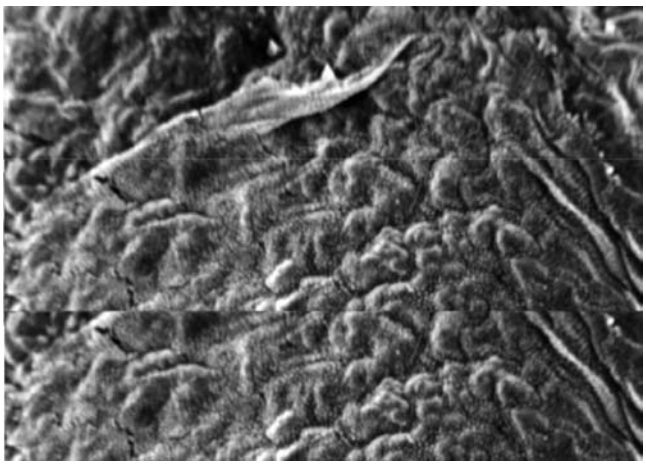

Figure 2. Epicardial surface of the RA. SEM. x 60.

Japan). Simultaneously, portions of tissue slices were frozen in liquid nitrogen to accomplish break-splits and the surfaces of these splits were treated with the method described above. The resultant preparations were studied and photographed using a scanning electron microscope (S-405A, Hitachi Medical Corp., Inc., Tokyo, Japan) at an accelerating strain 15 Sq. A part of the samples after studying in the scanning electron microscope was placed in an epon-araldite mixture following which they were cut into half-thin section with a thickness of 0.5-1.0 microns using an ultramicrotome (Ultracut, Reichert Jung, Austria). Subsequently the half-thin sections were stained with 1% solutions of methylene blue and fuchsine, studied and photographed with the light microscope. The results of scanning electron microscopy were compared with the results of light microscopy of histological and half-thin sections. In order to study the intraorgan vessels of the RA and its microcirculatory bed, the vascular system was filled with pre polymerized metacrilate via the coronary arteries. After polymerization of the injected mass, various segments of the heart were excised and put in a 30% solution of hydroxide-sodium for dissolving. The resultant corrosion casts of the vascular bed were carefully flushed with distilled water, dried in thermostat at temperature of 37 C. Following this, a thin layer of chemically pure gold was applied to the received samples surfaces using the ionization device, examined and photographed with the scanning electron microscope (S-405A, Hitachi Medical Corp., Inc., Tokyo, Japan).

RESULTS

The RA Epicardium

Histological features of normal human epicardium vary in different parts of the heart. First of all, concerns the superficial layer formed by mesothelial cells. Mesotheliocytes lay directly on a loose fibrillar layer of connective tissue. A thin homogeneous basal layer of mesotheliocytes can be seen at examination on electron microscopic level. Inside this loose fibrillar layer of connective tissue are located the nervous fibers, blood and lymphatic micro vessels. Larger vessels and clusters of fatty cells lay more deeply. The deep layers of loose connective tissue directly pass into myocardial endomysium. Outer surface of the RA wall is covered by a continuous layer of mesothelial cells. The SEM has shown that mesotheliocytes have the round-to-oblong form. At the tops of microrelief prominences they are large, closely adjacent to each other and the borders between them are not distinct. On the slopes of prominences and in grooves between them the cells are smaller, rather polymorphic. At high magnification the short, rare, round-to-oblong excrescences similar to microvilli can be seen on the apical surfaces of the majority of RA mesotheliocytes. (fig.1)

Sometimes roundish formations similar to the process of cells exocytose are located on the esotheliocytes apical parts. At the same time, connective tissue cells characterized by high electronic density are settled down in this region. Herewith, in the areas of the RA wall epicardium situated closer to the ventricle, one can find a rather large number of mesotheliocytes with usual, lengthened microvilli.

Our studies allow considering, that alongside with the mesotheliocytes with rounded, rare, short microvilli and mesotheliosytes with long, narrow-meshed microvilli, evenly settled down on the surface, there are also intermediate cells with rather small number of short and several long microvilli.

The microrelief of the RA wall outer surface is formed of the various size folds, grooves and separate prominences, without precise orientation. However, nevertheless it is possible to differentiate rather large folds of the 1st order having complex spatial geometry. Smaller folds of the 2nd order, without precise spatial orientation, can be found on their surface. High magnification allows to see even smaller, chaotically located folds of the 3rd order on their surface (Fig. 2).

The arrangement of epicardial folds in the area of the RA appendage essentially differs from this one in the area of its free wall. The microrelief is formed by large, longitudinal 1st order folds and smaller 2nd order folds, going perpendicularly to them. On these folds and in the grooves between them one

can recognize smaller 3rd order folds without precise orientation The study of the breaks and light optic preparations, especially of orientated half-thin sections, has shown the following. The 1st order folds are formed by the groups of superficial bunches of cardiomyocytes, the 2nd order folders – by connective tissue layer of epicardium, and the 3rd order folders – by bends of basal membrane, nuclei and microvilli of mesotheliocytes (Fig 3).

The RA Endocardium.

At light optic examination the main mass of all RA walls consists of myocardial muscles, with endocardium-covered inner surface. The endothelium with poorly developed basal layer (the basal membrane) can be recognized in the endocardium. A rather thin subendothelial layer is represented mainly by connective tissue fibers, contacting with cardiomyocytes. The blood vessels in the endocardium connective tissue layer are practically absent.

The SEM shows, that a rather thin endocardial connective tissue layer is formed by chaotically interlaced fibers. No traces of developed basal membrane can be found on the breaks of the RA wall. The inner surface of the RA free wall is covered by a continuous layer of endothelial cells with a rather smooth surface and individual, short prominences similar to microvilli. The endothelial cells densely adjoin to each other and do not form intercellular cracks on the borders. The inner surface of the RA free wall has a complex enough microrelief consisting from folds and grooves, with prominences and depressions. (Fig 4). Basically, it consists of three types of folds. The first type are rather large 1st order folds located in parallel to each other and oriented longitudinally in relation to the fibrous ring of the right atrioventricular valve. The smaller 2nd order folds seen on their surface, have no precise orientation, have a tortuous course and are divided by shallow grooves. At high magnification very fine, shallow and chaotically disposed 3rd order folds can be recognized through the entire surface.

The light optical researches of the RA appendage wall allowed to reveal, that its muscle bars, anatomosing and interlacing with each other, form a complex network.

Their inner surface is covered by the endothelium and, as a whole, the endocardium of the appendage does not differ from this one in other parts of the RA. A rather large number of microvessels can be found in the thickness of muscle layer. Due to anastomoses and interlacing of appendage muscle bars, the microrelief of its inner surface is made of large folds and grooves, which have different thickness and interconnect forming deep grooves and cavities (Fig.5). These large 1st order folds are orientated longitudinally in relation to the trabeculae course. On the surface of these large folds one can recognize smaller the 2nd order, located, mainly, in oblique or perpendicular directions in relation to the 1st order folds. At high magnification much smaller chaotically located 3rd order folds, also are revealed. The light optical study of the interatrial septum shows, that as a whole its hystoarchitectonics does not differ from the studied zones of the RA. The subendothelial connective tissue layer is a little bit thicker in this area. Here, as in the other parts of the atrium, the microvessels can be revealed. Strongly marked irregularity of the inner surface of interatrial septum is seen even in light optical. The microrelief of the inner RA surface of interatrial septum differs from the wall and appendage relief by presence of randomly directed rather large 1st order folds, anastomosed with each other. As a result the prominent areas of the septum surface similar to small islets, separated from each other by the deep grooves, are formed. The surface of these formations is finely tuberous, due to the presence of smaller, shallow 2nd order folds and the prominent areas between them. At high magnification the very fine, chaotically located 3rd order folds are seen on the whole surface of the interatrial septum. The endocardial cells, covering the septum, have the oval form with an even surface, with short microvilli on it. While these microvilli are not numerous, they are still more abundant than on the endothelial surface of the RA free wall.

The study of the breaks and orientated light optical preparations of different RA portions revealed, that its microrelief is formed with connective tissue fibers, as well as with the groups of its wall myocytes. The 1st order folds, as well as in epicardium, are formed by the groups of superficial bunches of cardiomyocytes, the 2nd order folds – by the connective tissue layer of endocardium, and the 3rd order folds – by the bends of basal membrane, nuclei and microvilli of endotheliocytes.

Microvascular system of the RA.

As shown by the study of corrosion preparations, the vascular system of the RA free wall muscular layer is composed by intraorgan vessels of various calibers, mainly aligned along the major axis of the atrium and microvessels parting from intraorgan vessels. (fig.6) The number of microvessels in the appendage is somewhat higher, than in the other portions of the RA.

The spatial organization of microvessels in the RA appendage is characterized by a certain long axis orientation. There are a lot of bifurcations and anastomoses. Many capillaries end in a blind fashion blindly in the appendage thickness or anastomose with each other through the sinusoids. The microvascular bed of the interatrial septum is characterized by a rather clearly expressed longitudinal orientation, the presence of dilatations in certain sites, blind ends and numerous anastomoses. The capillaries are more abundant, than in the RA free wall (fig.7). The density of the capillary network is similar to this one in the appendage, however there are less anastomoses. Herewith, unlike other portions of the RA, microvessels are present in the subendothelial layer. The sinusoids in all portions of the RA anastomose with a capillary network from all sides.

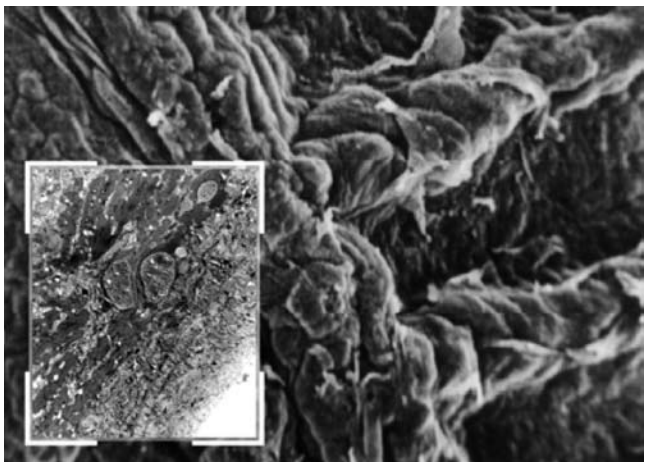

Figure 3. Epicardial surface of the RA appendage. SEM x 60.
In the box – the RA epicardium. A half-thin section.
Staining with methylene blue and fuchsine. 50 x 10.

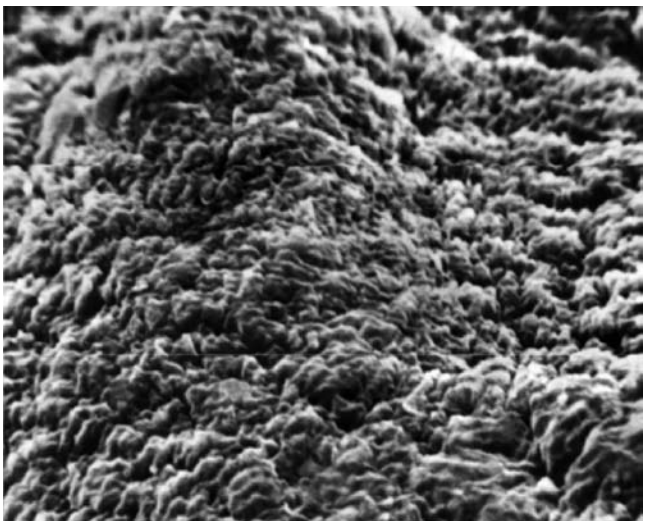

Figure 4. RA free wall. SEM x 200.

Figure 5. Inner surface of RA appendage. SEM x 75.

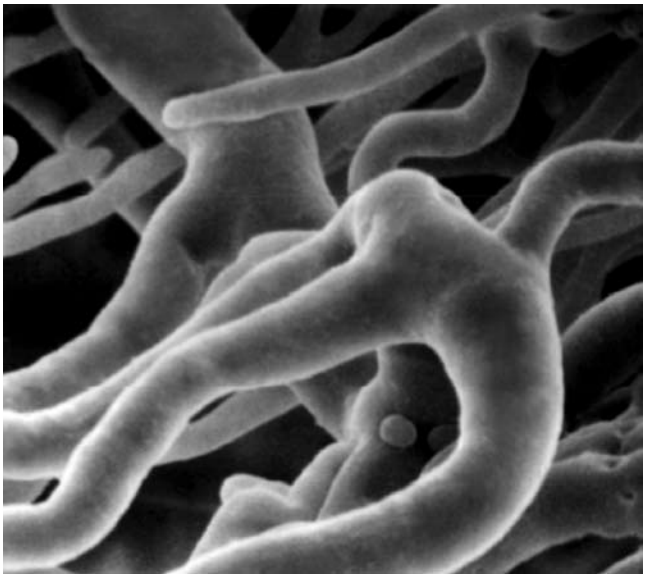

Figure 6. Vessels of the RA free wall.
Corrosion preparation. SEM x 1000.

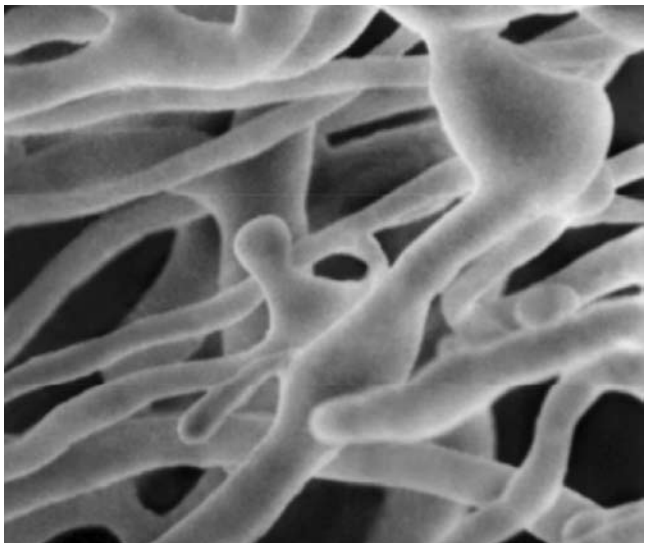

Figure 7. Vessels of the interatrial septum.
Corrosion preparation. SEM x 500.

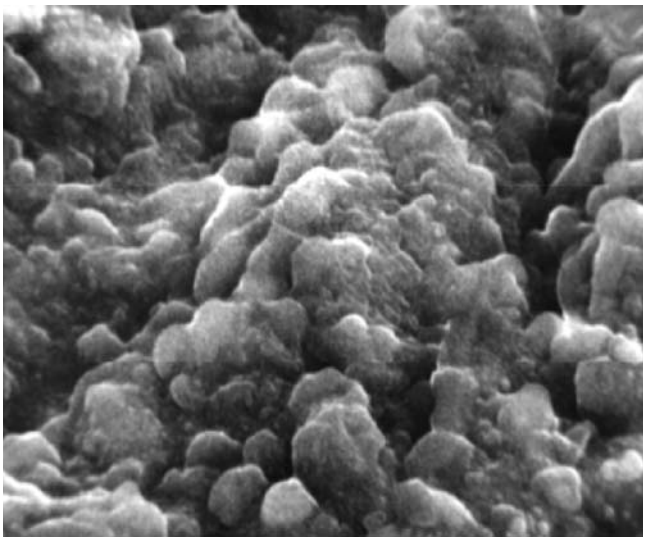

Figure 8. The surface of the CS wall. SEM. x 1000.

The coronary sinus.
Histological structure of the coronary sinus wall (CS) is typical for a large vein. It possesses a thin intimal layer, media, and a rather narrow adventitial layer. The microrelief of the inner surface of CS ostium is formed by medium-sized folds and crests with rounded tops. In the CS ostium the folds and crests have a circular disposition. Near the CS wall the folds and crests change their direction to longitudinal. As one can see on the CS wall breaks as well as in the sites deprived of endothelial cover and in half thin sections, numerous intimal fibers are interlaced and form a large-looped network. The folds and crests are planked by continuous endothelial layer. The luminal surfaces of the endotheliocytes are cupola-like (fig.8). One of the features of CS endothelial pavement consists in endotheliocytes' polymorphism. Their apical parts protruding in the lumen in some cells have the almost spherical form, while in others they are more flat. Single excrescences similar to microvilli are revealed on the cupola-like surfaces. A scarce number of folds can be seen on the surface of flat endotheliocytes. On a surface of endothelial pavement and in the sites deprived of endothelium there are few chylomicrons. Here they do not reach large sizes (fig.8)

DISCUSSION

The study of various portions of the RA with the use of light microscopy and SEM, as well as the study of vascular network in corrosion preparations, has allowed to reveal certain structural distinctions determining their morphological particularities. The study of half-thin sections from preparations investigated with SEM, has also allowed to verify and to estimate more accurately the data of SEM itself.

First of all, it concerns the microrelief of the inner surface of the RA, which being the most complex in the appendage, changes to more simple and uniform on its free wall surface. The endothelium of the interatrial septum is richer in microvilli, than the endothelium of the RA free wall. Three types of mesotheliocytes were revealed in the epicardium - with rounded, rare, short microvilli; with long, dense microvilli settled down on the surface with regular intervals; and intermediate cells with relatively small number of short and several long microvilli.

The microvascular microvessels are denser in the appendage and the interatrial septum. Microvascular networks in the appendage and the free wall are oriented on their long axis, while in the interatrial septum such orientation is absent. Besides, the microvessels of the subendothelial layer are found only in the interatrial septum.

Our researches have shown that the direction of folds of the CS inner surface varies. In the ostium the folds are oriented circularly, while in the sinus' trunk the orientation is longitudinal. Other feature of the CS consists in variable structure of the endothelial cells' lumen surface. Some cells have the cupola-like surface, while others are flattened. A relatively scarce number of small-sized chylomicrons are a distinctive feature of the CS. It was revealed that the different portions of the outer and inner RA surfaces have an original, individual microrelief with the folds varying in sizes, forms and directions. However there is a common principle of microrelief formation. This formation occurs with the participation of the endothelial or mesothelial pavements and the subjacent RA structures. Thus, the folds of 1st, 2nd and 3rd orders, differing by their directions, sizes and orientations, are formed, respectively, by the bunches of cardiomyocytes, epicardial or endocardial connective tissue layers, the basal membrane and endothelial or mesothelial pavements The spatial orientation and the character of the microrelief, as well as of subjacent connective tissue elements in these sites are determined by the hemodynamic, which, in its turn, cause the appropriate morphological structures. The spatial geometry of the microrelief of the outer or inner surfaces in various portions of the RA directly depends on muscle structures forming it. First of all it concerns the 1st order folds, formed by the groups of cardiomyocytes. Several groups of cardiomyocytes form large, visually accessible, trabeculae or muscle bars, which all together form the RA muscle layer. It is well traced while comparing the right atrial macro- and microstructures. (fig. 8). The complexity of spatial geometry of the RA microrelief is, in great part, caused by the complexity of three-dimensional anatomy of its muscle skeleton. The change of the typical microrelief during the reconstruction results in hemodynamic disturbances in the intervention area as compared with the initial state, and can result in the relevant complications, for example, thrombosis or microthrombosis. The use of various walls of the RA during surgical interventions should be made with the account not only of its macro-, but also microanatomy.

The preservation of microvascular networks of the RA walls will allow them to function adequately at reconstructive operations, for example as the pedicle flaps.

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Influence of Polymorphism in the ACE, PPARA, PPARD and NFATC4 Genes on the Clinical and Functional Characteristics of the "Athlete's Heart"

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INTRODUCTION

Besides physiological changes that are beneficial for health, the sport exercise cause specific cardiovascular pathology, which not only leads to early termination of the athlete's carrier but to his/her death (13, 17-20). According to foreign studies, cardiovascular mortality in athletes aged from 12 to 35 years is 2.5-fold higher than in non-sportsmen (18-19). In the opinion of the majority of foreign authors, the most common causes of sudden cardiac heart (SCH) in athletes include: hypertrophic cardiomyopathy (60%), structural abnormalities in coronary arteries (25%) and myocarditis (10%) (19-20). Timely diagnostics of these abnormal conditions is commonly difficult due to insufficient knowledge about the problems of "normal" and "abnormal" state in sports (17-19). The heart of most highly skilled athletes is known to have marked structural and functional features related to kind of sport, gender and possibly to genetic factors (4-7,16). Physiological changes in the "athlete's heart" can be so significant that they should be differentiated from abnormal structural changes caused by cardiomyopathies (10,13,17-19).

Currently, in addition to clinical and functional methods novel molecular genetic techniques are used to investigate the limits of individual adaptation to physical exercise. The sports geneticists have already revealed more than 130 hereditary determinants of success in a wide range of physical properties, which in combination allow individualizing physical loads in most kind of sports (8). On the other hand, the association between some of "athletic" genetic polymorphisms (ACE, PPARA, PPARD, and NFATC4) and a range of diseases was observed, i.e. hypertonic and coronary heart diseases, arrhythmias, type 2 diabetes mellitus and obesity (1,2,7,14). The specific combinations of these genetic factors not only affect the growth of sports results but cause the abnormal transformation of the "athlete's heart" due to the sports overexertion.

In our view, the most significant hereditary factors associated with the physical activity and probably involved in the physiological and pathological transformation of the "athlete's heart" are: polymorphism of the angiotensin converting enzyme gene (ACE), transcription factors of the peroxysome proliferator-activated nuclear receptors (PPARα-d) family genes and nuclear factors of activated T-cells genes (NFATC4). The brief summary of the range of functional activity of the above genes is presented in Table 1.

Therefore, the objective of our multi-stage study was to investigate the influence of the hereditary factors, associated with the physical activity (genetic polymorphism of *ACE, PPARA, PPARD*, and *NFATC4*) on morphological and functional properties of the cardiovascular system in highly qualified athletes.

Table 1. The range of functional activity of the polymorphisms in the (G/C) PPARA, (T/C) PPARD, (G/A) NFATC4 and (I/D) ACE genes.

Gene	Coded protein	Gene function	Class of polymorphism (rs SNP)
PPARA	PPARα	Regulates activity of the genes responsible for carbohydrate and lipid metabolism in the myocardium	rs 4253778 G
PPARD	PPARδ	Regulates activity of the genes responsible for metabolism of cholesterol, fatty acids oxydation	rs 2016520
NFATC4	Transcription factor NFAT	Regulates expression of many genes, including cytokines genes (TNF-a, IL 1,4,5)	rs 2229309
ACE	Angiotensin converting enzyme	Catalyses the conversion of angiotensin I into angiotensin II, regulating vascular tone	rs 4340

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MATERIAL AND METHODS OF THE STUDY

Sixty eight athletes (37 males and 31 females), aged 20 to 25 years, specializing in boat racing (n = 48) and all-round skating (n = 20) took part in the study. All athletes were members of the Russian Olympic Teams in boat racing and all-round skating or immediate reserve and were high class athletes: Master of Sports (MOS) (n = 56), World-Class Athlete (WCA) (n = 7), Honoured Master of Sports (HMOS) (n = 5). Control group for comparison of the results of genetic tests included 1073 persons (without sports experience), residents of Saint Petersburg, Moscow and Naberejnye Chelny (females 18 ± 0.1 years old, n = 585, males 18.6 ± 1.1 years old, n = 488).

Resting *electrocardiography (ECG)* was performed with the use of Alton (Russia) digital electrocardiogram recorder according to the common technique including analysis of the standard 12-lead recording. *Echocardiographic (Echo-CG)* assessment of morphological and functional characteristics of the myocardium in athletes was performed on Aloka-3500 ultrasound scanner with 3.5 MHz phased array transducer. The myocardium, cardiac valves and subvalvular structures were examined in M- and B-modes. The main measurements were performed in M-mode and B-modes. Interventricular septum thickness (IVST) in diastole, left ventricular posterior wall thickness (LVPWT), left ventricular end-diastolic and end-systolic diameters (LVEDD, LVESD), left ventricular end-diastolic and end-systolic volumes, left ventricular myocardial mass (LVMM, g) and LVMM index (LVMMI, g/m^2) were assessed.

The assessment of maximal oxygen consumption in rowers was performed using PM 3 (Concept II, USA) mechanical row ergometer during the test with increasing work load. The assessment of maximal oxygen consumption (Max V_{O2}, L/min or ml/min/kg) in ice-skaters was performed on the cycle ergometer with increasing work load. Gas exchange parameters and heart rate (HR, beats per minute - bpm) were continuously recorded in the course of the test (MetaMax 3B gas analyzer, Cortex, Germany).

DNA extraction: Subjects' DNA samples extracted with adsorption technique or alkaline extraction technique depending on the method of collection of biological samples were used for molecular genetic analysis (1).

Genotyping: The polymorphisms in the *ACE, NFATC4, PPARA* and *PPARD* genes were detected using polymerase chain reaction with subsequent restriction assay according to the techniques described above (1,2,4,7).

Statistical processing was performed using GraphPad InStat software program. The following parameters were assessed: mean values (*M*), standard error (±*SEM*) and mean standard deviation (*s*). The significance of the differences in the allele rate between the samples compared was assessed using χ^2-test. The quantitative comparison (echocardiographical and physiological parameters) was performed with the use of unpaired t-test. The differences were considered statistically significant with $p < 0.05$.

The abbreviations used in the article are the following: IVSD (cm) – interventricular septum thickness in diastole ; LVIDd (cm) – left ventricular (LV) internal diameter in diastole; LVPWd (cm) - left ventricular posterior wall thickness in diastole; LVIDs (cm) – LV internal diameter in systole; VO_2/kg – ratio of the maximal oxygen consumption to body weight.

RESULTS OF FUNCTIONAL EXAMINATIONS

Normal ECG recordings were observed in 48% examined athletes; slight changes (vegetative and visceral dysfunction syndrome, atrial rhythm and sporadic atrial extrasystoles) were revealed in 42% athletes. Five (7%) athletes had ECG signs of left ventricular hypertrophy. Wolf-Parkinson-White (WPW) ECG-phenomenon was observed in 3 (3%) subjects. Echocardiographic evaluation revealed the following: left ventricular posterior wall thickness (LVPWT) and interventricular septum thickness (IVST) was up to 12.0 mm and the end-diastolic volume (EDV) was 45.0 to 55.0 mm in 17 (25%) athletes (5 males and 12 females). According to Maron et al. (13,17-18), this may be regarded as the variant of the "physiological athlete's heart"; hypertrophy with LVPWT and IVST of 12 to 17 mm and EDV 41 to 58 mm was observed in 51 athletes (75%, 31 males and 20 females).

Our study was mainly focused on the investigation of the functional characteristics of the physiological and pathological "athlete's heart". As was said, the main feature of the "athlete's heart" is the physiological myocardial hypertrophy, which must not exceed 12 mm, according to the authorities in sports cardiology (17-18). The second feature of the physiological "athlete's heart", which is at least equally important, is a slight increase in LVEDD (up to 55 mm), not exceeding the critical value of 60 mm (18). In our study the physiological (up to 12 mm) increase in LVPWT was only observed in 25% athletes. In 75% subjects LVPWT increased to 12 17 mm. No subject had the increase in EDD exceeding the critical value of 60 mm as well as signs of myocardial dysfunction.

The comparison of the electrocardiographic and echocardiographic data revealed the following phenomenon: ECG signs of right ven-

tricular and left ventricular hypertrophy were only observed in 5 athletes, which is inconsistent with the echocardiographic data, suggesting significant (more than 12.0 mm) increase in the LVPWT and IVST in 51 athletes. In our case the subgroup with the electrocardiographic signs of myocardial hypertrophy consisted solely of males with high sport skill category (3 World-Class athletes and 2 Honoured Masters of Sports), members of the Russian picked teams in rowing (4) and speed skating (1).

Therefore, *in the course of the functional evaluation we distinguished 5 groups of athletes*: 2 subgroups (males and females) with LVPWT up to 12 mm, 2 subgroups (males and females) with LVPWT > 12 mm and 1 subgroup (males) with ECG signs of myocardial hypertrophy of LVPW. Characteristics of the above subgroups are presented in Table 2.

1. Genetic research data in the subgroup of female athletes (n = 32)

At the first step, the statistical analysis of the above mentioned gene alleles distribution was performed in the subgroup of the female athletes with LVPWT less than and more than 12 mm. The comparison of the percentage of four studied gene alleles in female athletes with LVPW hypertrophy > 12 mm, without hypertrophy and in the control group is presented in Table 4.

According to submitted data, the *ACE, PPAR* a-d, *NFATC4* alleles distribution in the subgroups of females was as follows: significant differences in allele I (ACE) distribution were observed between the subgroups and as compared to the control group; the subgroup with LVPWT > 12 mm showed a higher percentage, while in the subgroup with LVPWT < 12 mm significant reduction of this allele was observed as compared to the control group.

No significant differences in the PPARA, PPARD and NFATC4 allele distribution were revealed.

2. Genetic research data in the subgroup of male athletes (n = 36)

At the second step, statistical analysis of the allele distribution of the above mentioned genes was performed in the subgroup of male athletes with LVPWT less than and more than 12 mm. The comparison of the percentage of four studied gene alleles in male athletes with LVPW hypertrophy > 12 mm, without hypertrophy and in the control group is presented in Table 5.

Significant increase in the percentage of allele I (ACE) in male athletes with myocardial hypertrophy (LVPWT > 12 mm) was revealed along with the reduction of percentage in the subgroup of athletes with LVPWT < 12 mm. We also observed significantly higher percentage of the allele A (NFATC4) in the subgroup with LVPWT > 12 mm as compared to the subgroup without hypertrophy as well as to the control group. No significant differences in the PPARA and PPARD allele percentage distribution between two compared subgroups were revealed.

3. Results of genetic research in two subgroups of male athletes with hypertrophy > 12 mm (n = 31): in a subgroup with almost normal ECG (n = 26) and in athletes with ECG signs of myocardial hypertrophy (n = 5).

The investigation of the factors causing inversion of the terminal part of QRST complex ("myocardial dystrophy due to physical overexertion", according to Dembo) is of a great interest for practical medicine. In our case the subgroup with ECG signs of myocardial hypertrophy consisted solely of males with high sports skill category (3 World-Class athletes and 2 Honoured Masters of Sports), members of the Russian picked teams in rowing (4) and speed skating (1).

At the third step of our study we have compared the morphological and genetical characteristics in 2 groups of highly skilled male athletes: with and without T wave inversion. Data on sports discipline, qualifications, height and weight parameters in these 2 subgroups, as well as the results of complex examination are presented in Tables 6 – 8.

According to the data presented in Tables 6 and 7, the two compared subgroups were identical by age, height/weight and morphological/functional characteristics. Echocardiographic data showed symmetrical myocardial hypertrophy, LVPWT exceeding the limits of physiological hypertrophy (12 mm) in all athletes. The results of genetic screening in these 2 subgroups are presented in Table 8.

Comparison of percentage distribution of genetic polymorphism in two above subgroups revealed significantly higher percentage of allele A (NFATC4) in the subgroup with T wave inversion as compared to the subgroup without inversion and to the control group (Figure 2). We also revealed that the subgroup with T wave inversion tended to have higher percentage of allele I (ACE) ($0.07 < p < 0.08$) as compared to the group without inversion. The percentage of allele D in the group with T wave inversion was lower than that in the group without inversion. No significant differences between the subgroup in the PPARA and PPARD alleles distribution were observed.

Results of correlation analysis The analysis of correlations performed in the study revealed statistically significant ($r = 0.62$) positive correlation between the percentage of I allele (ACE) and the value of left ventricular end-diastolic

Table 2. Characteristics of compared subgroups by kind of sports, qualifications, age and anthropometric data.

Compared subgroups	Number (n)	Kind of sports	Qualifications	Age (years) M±sem	Height (cm) M±sem	Weight (kg) M±sem
Female athletes with LVPWT > 12 mm	20	4 ice-skaters + 16 rowers	2 candidate master (CM) + 16 MOS + 2 WCA	20.8± 2.0	177.2±2.3	71.7±1.0
Female athletes with LVPWT < 12 mm	12	5 ice-skaters + 7 rowers	2 CM + 10 MOS	18.8± 2.2	175.2±1.5	69.2±2.2
Male athletes with LVPWT > 12 mm	31	10 ice-skaters + 21 rowers	5 HMOS+ 5 WCA + 20 MOS + 1 CM	21.8± 0.8	189.5±1.2	86.6±1.1
Male athletes with LVPWT < 12 mm	5	2 ice-skaters + 3 rowers	5 MOS	19.8± 2.1	185.2±2.5	85.3±2.1
Athletes with T wave inversion	5	1 ice-skater + 4 rowers	1 WCA + 4 HMOS	22.3± 0.2	185.8±2.3	85.7± .5

Table 3. Echocardiographic and ergospirometric data in 5 subgroups of athletes.

Compared subgroups	IVSD (cm) M±sem	LVIDd (cm) M±sem	LVPWd (cm) M±sem	LVIDs (cm) M±sem	Vo2/kg (ml/min) M±sem
Female athletes with LVPWT > 12 mm	1.13±0.01	4.56±0.02	1.32±0.03	2.98±0.01	45.8±3.2
Female athletes with LVPWT < 12 mm	1.07±0.04	4.71±0.01	1.01±0.01	3.04±0.02	48.2±2.2
Male athletes with LVPWT > 12 mm	1.41±0.03	5.02±0.03	1.44±0.02	3.42±0.01	59.5±2.3
Male athletes with LVPWT < 12 mm	1.24±0.01	4.84±0.01	1.10±0.01	3.20±0.02	57.4±2.4
Athletes with T wave inversion	1.40±0.02	5.03±0.01	1.43±0.03	3.30±0.03	60.0±3.2

Table 4. Comparison of the ACE, PPARA, PPARD and NFATC4 alleles frequency distribution in females with myocardial hypertrophy > 12 mm, without hypertrophy and in the control group.

	ACE	Allele frequency (%)	PPARA	Allele frequency (%)	PPARD	Allele frequency (%)	NFATC4	Allele frequency (%)
Female athletes with LVPWT > 12 mm	I	72.5*	G	87.5	T	82.5	G	45
	D	27.5*	C	12.5	C	17.5	A	55
Female athletes with LVPWT < 12 mm	I	37.5 *	G	83.3	T	79.2	G	45.8
	D	62.5*	C	16.7	C	20.8	A	54.2
Control	I	48.5	G	83.2	T	89.7	G	43.6
		51.5	C	16.8	C	10.3	A	56.4

* - significant differences between the subgroups and compared to the control group ($p < 0.05$)

Table 5. Comparison of the ACE, PPARA, PPARD and NFATC4 alleles frequency distribution in males with myocardial hypertrophy > 12 mm, with and without ECG signs of asymmetrical hypertrophy and in the control group.

	ACE	Allele frequency (%)	PPARA	Allele frequency (%)	PPARD	Allele frequency (%)	NFATC4	Allele frequency (%)
Male athletes with LVPWT > 12 mm	I	59.6*	G	88.5	T	92.3	G	34.6*
	D	40.4*	C	11.5	C	7.7	A	65.4*
Male athletes with LVPWT < 12 mm	I	30*	G	90	T	90	G	40*
	D	70*	C	10	C	10	A	60*
Control	I	48.5	G	83.2	T	89.7	G	43.6
	D	51.5	C	16.8	C	10.3	A	56.4

* - significant differences between the subgroups and compared to the control group ($p < 0.05$)

Table 6. Basic data concerning the qualification, sports discipline, age and anthropometric features in the compared groups (*).

Compared subgroups	Number (n)	Sports discipline	Qualifications	Age (years) M±sem	Height (cm) M±sem	Weight (kg) M±sem
Athletes without T wave inversion	26	9 ice skaters + 17 rowers	1 HMOS+4 WCA +21 MOS	21.8± 0.8	189.5±1.2	86.6±1.1
Athletes with wave T inversion	5	1 ice-skater + 4 rowers	1 WCA + 4 HMOS	22.3± 0.2	185.8±2.3	85.7± .5

* - no significant differences between the groups ($p > 0.08$)

Table 7. Basic echocardiographic and ergospirometric characteristics in the compared subgroups (*).

Compared subgroups	IVSD (cm) M±sem	LVIDd(cm) M±sem	LVPWd(cm) M±sem	LVIDs(cm) M±sem	Max VO2 (ml/min/kg) M±sem
Athletes without T wave inversion	1.41±0.03	5.02±0.03	1.44±0.02	3.42±0.01	59.5±2.3
Athletes with wave T inversion	1.40±0.02	5.03±0.01	1.43±0.03	3.30±0.03	60.0±3.2

* - no significant differences between the groups ($p > 0.08$)

Table 8. Comparison of the ACE, PPARA, PPARD and NFATC4 alleles frequency distribution in males with (n = 5) and without (n = 26) T wave inversion on ECG.

	ACE	Allele frequency (%)	PPARA	Allele frequency (%)	PPARD	Allele frequency (%)	NFATC4	Allele frequency (%)
Athletes without T wave inversion	I	59.6**	G	88.5	T	92.3	G	34.6*
	D	40.4**	C	11.5	C	7.7	A	65.4*
Group with T wave inversion	I	66.7**	G	91.6	T	100	G	25*
	D	33.3**	C	8.4	C	0	A	75*
Control	I	48.5	G	83.2	T	89.7	G	43.6
	D	51.5	C	16.8	C	10.3	A	56.4

* - significant differences between the subgroups and compared to the control group ($p < 0.05$)

** - significant differences between the groups with $0.07 < p < 0.08$

diameter (LVEDd) and between the A allele (NFATC4) and the left ventricular posterior wall thickness in diastole (LVPWd) (r = 0.65).

DISCUSSION

The analysis of obtained results revealed significant differences in the distribution of two out of four studied polymorphisms in highly skilled athletes: ACE gene I/D polymorphism and NFATC4 gene G/A polymorphism. The percentage of I allele (ACE) was higher in the subgroup with left ventricular myocardial hypertrophy > 12 mm in both female and male athletes. The analysis of the distribution of NFATC4 gene G/A polymorphism revealed significant increase in the percentage of A allele in males with myocardial hypertrophy as compared to the subgroup without hypertrophy and to the control group.This fact confirms the opinion of several authors about the particular importance of the above genes in the transformation of the cardiovascular system under the influence of the functional stress (4-6,11,14,15). The myocardial hypertrophy is known to be associated with significant changes in gene expression in the cardiomyocytes (12, 14). The studies showed that the functional stress potentiates the expression of many genetic sequences. The most important are the genes of renin-angiotensin-aldosteron system (RAAS) and the genes of calcineurin signal pathway. There is an opinion suggesting that reorganization of hormonal regulation in the form of stress reaction with the increase of renin-angiotensin aldosteron system (RAAS) activity plays the important role in genesis of both physiological and pathological changes in myocardium of athletes (11). The resulting hemodynamical stress, caused by RAAS hyperactivation contributes to the proliferation of myocardial connective tissue structures (type I collagen) with subsequent decrease of its elasticity (21), resulting in ineffective hypertrophy and pathological dilation of the “athlete’s heart” in parallel with the decrease of its functional activities. The observed correlation between the percentage of I allele of ACE gene and the left ventricular end-diastolic diameter supports the opinion about the possible influence of ACE gene on the processes of the stress-induced changes in myocardium, including that in athletes.

On the other hand, the observed increase in the percentage of A allele of the NFATC4 gene in athletes with myocardial hypertrophy of the left ventricular posterior wall > 12 mm, as well as its significant correlation with the LVPW thickness, suggest involvement of A allele (NFATC4) in formation of left ventricular myocardial hypertrophy in athletes. Our results are consistent with the current opinion that the specific activation of calcineurin and its downward effector NFATC4 is a sufficient factor inducing the formation of hypertrophic reaction in mammalians (2,14). The target genes of the transcription factors of the NFAT family include the interleukin-1, -4, -5 genes (IL1, IL4, IL5; immune response); tumor necrosis factor alpha (TNF; immune response) gene; atrial and brain natriuteric peptides gene (ANF, BNF; hypertrophic myocardial response); insulin-like growth fac-

tor 1 gene (IGF1; growth and regeneration of the skeletal muscles) and others (2-14). According to Molkentin et al. (13) the level of cytoplasmatic Ca^{2+} in the cardiomyocytes increases in response to the growth factors, thus stimulating the calcineurin/calmodulin-dependent protein phosphatase – calcineurin. In turn, this substance stimulates the cytoplasmatic factor NFATC4 that causes (due to its translocation into the nucleus) the activation of transcription of various structural and regulatory genes, including cytokines TNF-alpha and IL-1, -4, -5 genes. A previously established relation between the NFATC4 gene and the physical activities (2), as well as the observed increase of the percentage of A allele of NFATC4 gene in highly skilled athletes with myocardial hypertrophy > 12 mm, and the correlation between this allele and the value of the LVPWT confirm these hypothesis.

In our study we focused on the analysis of the causality of significant ECG-changes in 5 highly skilled athletes with confirmed asymmetrical myocardial hypertrophy. In the course of interpreting the results of our study, we assumed the opinion of the reputed foreign cardiologists, believing that moderate symmetrical hypertrophy of the right and left heart represents physiological changes in athletes. The presence of ECG signs of myocardial hypertrophy in athletes along with the absence of echocardiographically confirmed asymmetric hypertrophy suggest the antemorphological involvement of either right or left heart and may predict the formation of the "pathological athlete's heart" (16-18). The comparison of anthropometric parameters and the structural and functional features of the cardiovascular system in these athletes and in athletes with the myocardial hypertrophy not associated with ECG-changes, did not reveal any significant differences between the groups. However, the analysis of the genotype distribution revealed significant increase in the percentage of A allele of NFATC4 gene in this subgroup. Assuming the influence of A allele (NFATC4) on the extent of hypertrophic response in experimental animals (13), as well as the previous data concerning involvement of this gene protein expression (TNF-alpha) in the formation of immune-regulatory dysfunction in young athletes with decreased functional abilities of the oxygen transfer system (3-4,22), we suggest that the carriage of A allele (NFATC4) is a negative prognostic factor for athletes, since its possible activation under the influence of the sport overexertion and hypoxic stress results in the expression of factors, involved in the pathological stress-induced transformation of the "athlete's heart".

CONCLUSIONS

1. Significant differences in the distribution of ACE gene I/D polymorphism and NFATC4 gene G/A polymorphism between the subgroups of athletes with and without myocardial hypertrophy were revealed. Significantly higher percentage of I allele (ACE) and A allele (NFATC4) in the subgroups with myocardial hypertrophy was observed.
2. The correlations were observed between I allele (ACE) and the left ventricular end-diastolic diameter (r = 0.62), as well as between A allele (NFATC4) and the left ventricular posterior wall thickness in diastole (r = 0.65) in athletes, suggesting involvement of these genes in the formation of the specific features of the "athlete's heart".
3. The higher percentage of A allele (NFATC4) and I allele (ACE) in athletes with myocardial hypertrophy with LVPWT > 12 mm and with T wave inversion suggests possible involvement of these alleles in the stress-induced changes in the electrogenesis in the cardiac muscle of athletes under the influence of the sports overexertion.

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